PROGRESS VOLUME

An Integrated Practice of Medicine

PROGRESS VOLUME

Modern Developments in Therapeutics and Methods of Treatment

TO ACCOMPANY

An Integrated PRACTICE OF MEDICINE

By Harold Thomas Hyman, M D

W B SAUNDERS COMPANY

Philadelphia & London

1950

MADE IN U S A

PRESS OF W B SAUNDERS COMPANY

PHILADELPHIA

READER S GUIDE

This *Progress Volume* which is a supplement to *An Integrated Practice of Medicine* summarizes recent and pending contributions to the medical sciences It covers the period between press time for the original set and the present

In general new material is concerned with recently devised therapeutic measures and with improved methods for specific management of the individual patient Of newer therapeutic preparations and modalities principal interest centers on ACTH (anterior pituitary adrenocorticotropic hormone) adrenal cortical extract (Cortone cortisone compound E) Antabus antihistamines aureomycin chloramphenicol (Chloromycetin) Dicumarol heparin suramin sodium products used in the prevention and treatment of tuberculosis (BCG vaccine the streptomycins para aminosalicylic acid and thiosemicarbazones) sulfonamides sulfones Terramycin and tyrothricin

In the descriptions of various therapeutic agencies names of manufacturers dosage forms and package information are provided It is useful to the practicing physician to know the names of manufacturers of newer drugs and the various forms in which they are available

Despite efforts to confine recommendations to Council approved products it has been nece sary to include many useful unofficial preparations in this *Progress Volume* Anticipation of Council action somewhat compensates for the nece sary lag between delivery of manuscript and publication date Adoption of this policy in preparation of earlier volumes of the *Integrated Practice of Medicine* enabled readers to keep ahead of many medical accomplishments without significant jeopardy since the text clearly differentiated between accepted products and those to which approval had not yet been accorded Retention of obsolete or obsolescent preparations in listing drugs and pharmaceuticals has been adopted to give the reader a complete roster with cogent reasons why older products have been superseded by more potent and/or le s toxic preparations

With the introduction of new anti infective agents treatment of many frequently encountered infections has been changed In consequence general principles and practical management of almost all infectious diseases have been reconsidered

In addition to fresh surveys of the management of commonly encountered clinical infections the therapy of patients afflicted with rare microbic disease entities also has been re assessed

For more complete understanding of the principles of therapy in infection the reader is urged to study the *Introduction* and the collec

tive essays entitled *Allergy Adrenal Cortical Extracts and Anterior Pituitary Adrenocorticotropic Hormones* and *Anti Infective Therapy* The *Introduction* particularly describes hazards due to antithera peutic devices secondary to introduction of antibiotic agents the material on *Allergy* emphasizes the havoc wrought by hypersensitivity of host tissues to protoplasm of invading parasites and/or protein moieties derived from therapeutically introduced products the section devoted to *Adrenal Cortical Extracts and Anterior Pituitary Hor mone* integrates the concepts of hypersensitivity and hormonal dis equilibrium and suggests the boons and future potentialities of *Artificially Induced Therapeutic Hypercortinism* and finally the summary of *Anti Infective Therapy* gives body to the claim that the past two decades constitute a Golden Age of Therapeutics

Apart from reassessment of the mechanisms and management of syndromes secondary to hypersensitivity to bacteria and therapeutic agents the sections on Allergy and on Adrenal Cortical Extracts and Anterior Pituitary Hormone perform a similar service for a variety of clinical entities actually or potentially re ponsive to Artificial Hyper cortinism

The monumental contributions to patient management in infectious and allergic diseases do not constitute isolated accomplishments of the Golden Age of Therapeutics Tremendous advances also have been registered in the treatment of neoplastic disturbances and especially in the management of various manifestations of endovascular throm bosis including the frequently encountered and menacing syndromes of phlebothrombosis thrombophlebitis coronary and cerebral occlu sions and embolic accidents

In an effort to give three-dimensional coverage to clinical medicine each presentation is initiated by a summary of *General Principles of Diagnosis and Therapy* particularly emphasizing recent contribu tions These general statements are followed by specific details as to *Immediate Care* for guidance of the physician summoned to treat the patient at the onset of an illness At this first visit the medical prac titioner projects a tentative diagnosis on the basis of presenting symp toms and signs since laboratory data are not yet available if they are to be obtained at all In an infectious disease for example immediate tentative suggestions constitute *Probatory Anti Infective Therapy* by which the patient is given the advantage of intensive treatment during the opportune moments of early invasion The practitioner orders or administers that antibiotic which in his judgment seems most likely to overcome the particular living micro-organism assumed to be the etiologic factor in the disea e In situations of mild to moderate intensity and when symptoms and s gns point relatively conclusively to the nature of the offending invader reliance is placed on a single anti biotic However in graver emergencies *Desperation Anti Infective*

Therapy is employed for blanket coverage of the bacterial spectrum through simultaneous use of several antibiotics Negligible toxicity of most newer anti infective agents permits the practice of *Desperation Anti Infective Therapy* at minimum risk for maximum gain

Together with *Immediate* Care of the afflicted patient the reader will note directions for household or communal prophylaxis implement ing the concept that the practitioner holds the first line of defense in preventive medicine and preventable mortality

Suggestions for *Immediate Care* are followed by those for *Con tinuing Care (Favorable Course)* for *Continuing Care (Unfavorable Course)* and for *Continuing Care (Progressively Unfavorable Course)* This fluid approach to patient management recognizes the practical truth that it is not for Calm Seas and Prosperous Voyage that the seasoned colleague seeks assistance from the printed text Rather he employs his library consultant when he is beset and bedevilled by dif ficulties idiosyncrasies complications and untoward events

Under *Continuing Care (Favorable Course)* it is assumed that the tentative diagnosis has proven correct and that probatory suggestions for therapy have been successful in mitigating or eliminating present ing symptoms and signs Under these circumstances the practitioner need only provide for maintenance of the regimen and for guidance of the patient through convalescence

When at his return visit the practitioner finds that favorable progress has not been made he resorts to suggestions summarized under the heading *Continuing Care (Unfavorable Course)* Under these cir cumstances the tentative diagnosis may have been incorrect the admin istered drug may have been given in insufficient quantity the patient may have revealed idiosyncrasy or toxic responses complications may have supervened surgical indications may have arisen or any of innum erable imponderables which go into the mechanisms of disease may have been interpolated alike to the discomfort of patient and physician At this time the physician nece sarily must take stock He may obtain assistance from the laboratory it may be necessary to discontinue the originally administered drug and sub titute another he may increase the dose of the original drug or give it by another route either intra muscularly or intravenously he may combine the original drug with a cumulative or synergistic product or he may concentrate on time honored symptomatic treatment for the relief of particularly disturbing subjective manifestations

When the physician observes a *Progressively Unfavorable Course* his ingenuity is challenged He is required to muster all of his thera peutic equipment in order to combat the jeopardies that imperil the comfort and life of his patient Under these circumstances he may seek consultation with a more seasoned internist or the indicated specialist he may hazard what Hippocrates called desperation remedies and

administer increasingly large doses of drugs previously employed he may resort to new remedies with which he may have had little or no previous experience or he may fortify the defenses of his patient by infusion or transfusion in order to combine all efforts to turn the tide in favor of the afflicted

In presentations of patient management the reader will observe that the Progress Volume does not pretend to absolute knowledge The seasoned physician familiar with the many imponderables of medical practice realizes that no one individual and no group of individuals rightly can claim possession of the correct answer or knowledge of optimum therapy An attainable goal however is that of guidance in the evolution of a satisfactory method of management for the presenting clinical problem as it is manifest in the individual patient

For convenience the text of the Progress Volume is alphabetized according to principal therapeutic modalities and outstanding clinical syndromes The former are distinguished by main side heads the latter are introduced by main center heads

Fusion of the Progress Volume with the original set has been accomplished by continued adherence to the concepts of Integrated Medical Practice and Individualization of Patient Management by the Physician by numerous page references interpolated in the text and by inclusion in this volume of Indexes to Illustrations and Differential Diagnosis by Main Presenting Signs and Symptoms and the General Subject Index to Volumes I to IV

Finally a separate Index to the Progress Volume also is appended distinguished by its appearance on tinted paper

Cumulatively the indexes are master keys which open many doors Meticulously assembled they provide the inquiring reader with immediate and complete access to text charts and illustrations of all five volumes Intelligently used they function as guides from presenting symptom through differential diagnosis to symptomatic or specific treatment

If the texts of the Progress Volume and of the previously published four volumes have been collected and presented as formulated they will implement the basic philosophic concepts of the biologic unity of man's ills the integration of medical practice and the necessarily anthropocentric approach to complete medical management This single reference source should function as a library or desk consultant giving access to possible solutions of problems presented by individual patients With the Integrated Practice of Medicine and its Progress Volume at hand the reader may feel secure in the knowledge that he has at his disposal a precise and concise guide to present methods of effective therapy Moreover he should have been prepared psychologically and pharmacologically to appraise new contributions to reject the spurious and readily to include pending accomplishments in his therapeutic repertory

HAROLD THOMAS HYMAN M D

October 1960

CONTENTS

*For reference to specific drugs see the Index to the Progress Volume p 4847

administer increasingly large doses of drugs previously employed he may resort to new remedies with which he may have had little or no previous experience or he may fortify the defenses of his patient by infusion or transfusion in order to combine all efforts to turn the tide in favor of the afflicted

In presentations of patient management the reader will observe that the Progress Volume does not pretend to absolute knowledge The seasoned physician familiar with the many imponderables of medical practice realizes that no one individual and no group of individuals rightly can claim possession of the correct answer or knowledge of optimum therapy An attainable goal however is that of guidance in the evolution of a satisfactory method of management for the presenting clinical problem as it is manifest in the individual patient

For convenience the text of the Progress Volume is alphabetized according to principal therapeutic modalities and outstanding clinical syndromes The former are distinguished by main side heads the latter are introduced by main center heads

Fusion of the Progress Volume with the original set has been accomplished by continued adherence to the concepts of Integrated Medical Practice and Individualization of Patient Management by the Physician by numerous page references interpolated in the text and by inclusion in this volume of Indexes to Illustrations and Differential Diagnosis by Main Presenting Signs and Symptoms and the General Subject Index to Volumes I to IV

Finally a separate Index to the Progress Volume also is appended distinguished by its appearance on tinted paper

Cumulatively the indexes are master keys which open many doors Meticulously assembled they provide the inquiring reader with immediate and complete access to text charts and illustrations of all five volumes Intelligently used they function as guides from presenting symptom through differential diagnosis to symptomatic or specific treatment

If the texts of the Progress Volume and of the previously published four volumes have been collected and presented as formulated they will implement the basic philosophic concepts of the biologic unity of man's ills the integration of medical practice and the necessarily anthropocentric approach to complete medical management This single reference source should function as a library or desk consultant giving access to possible solutions of problems presented by individual patients With the Integrated Practice of Medicine and its Progress Volume at hand the reader may feel secure in the knowledge that he has at his disposal a precise and concise guide to present methods of effective therapy Moreover he should have been prepared psychologically and pharmacologically to appraise new contributions to reject the spurious and speedily to include pending accomplishments in his therapeutic repertory

HAROLD THOMAS HYMAN M.D

October 1960

Therapeutic Agents

Clinical Syndromes

Therapeutic Agents

Clinical Syndromes

INTRODUCTION

In the years which followed the publication of the Integrated Practice of Medicine concepts and terminology concerning allergy (hyper sensitivity) have changed to a considerable degree Although Allergy will be dealt with at length under that heading it seems appropriate to discuss here in general terms phenomena like histamine type and tuberculin type hypersensitivity bacterial resistance antitherapeutic factors and drug allergens—disease conditions and factors which will be encountered frequently throughout this volume

MICROBIC IMMUNITY (BACTERIAL FASTNESS TO ANTIBIOTICS)

The practitioner has first hand familiarity with the development of bacterial resistance to anti infective agents Shortly after introduction of sulfonamide most clinicians noted a progressively diminishing cure rate in statistical studies of gonorrheal urethritis In the laboratory this disquieting observation was proven to be the result of development by the micro-organism of active immunity to the therapeutic agent

The phenomenon of sulfonamide fastnes exhibited by gonococci unfortunately proved neither an unique nor an infrequent antithera peutic reaction A principal difficulty attending the conquest of the tubercle bacillus by the streptomycins is that of acquired immunity to the antibiotic as shown by development of a not insignificant per centage of treatment resistant acid fast invaders

In the macrocosm occurrence of this antitherapeutic property is observed in the reactions of the common housefly to insecticides con taining DDT Approximately 5% of the e pests and potential vectors of di ease become DDT fast and what is worse they propagate a race of offspring that inherits this same antitherapeutic property

Quite likely bacterial fastness or resistance is a universal biological phenomenon exhibited in greater or le ser degree to all anti infective agents To the best of present knowledge microbic active immunity develops most prominently on exposure to sulfonamide and strep tomycin le s so to penicillin and eemingly least of all to aureomycin bacitracin and chloramphenicol

Elsewhere the relationship between the mechanisms of *active immunity* and *hyper ensitivity* is fully discussed (p 4165) At this point it is sufficient to note that tho e bacteria (streptococci tubercle bacilli) most capable of developing active immunity to antibiotics are also most likely to produce hypersensitivity phenomena in the human ho t An exception to this general rule is the gonococcus which though it rapidly becomes sulfonamide fast does not appear to produce ignifi cant histamine type or tuberculin type hypersensitivities in man

Specificity At least six observations pertinent to acquired bacterial immunity have practical implications

clinician is familiar with the first of these particularly in trichinosis where initial clinical manifestations include angioneurotic edema and eosinophilia the second and more serious tuberculin type reaction is especially illustrated by the rheumatic fever syndrome following sensitization of the patient to the bacterial protein of invading streptococci (p 4493)

Acute Histamine-type Hypersensitivity to Bacterial Allergen

In acute histamine type reactions to bacterial allergen the tissue response occurs shortly after exposure to the microbe The ensuing reaction is characterized by increased vessel permeability edema eosinophilia and spasm of smooth muscle Anaphylactic antibody is demonstrable in circulating blood and is transferable to the experimental animal (Prausnitz Kustner reaction) histamine injection partially recreates the hypersensitivity syndrome and antihistamines afford palliation

Chronic Tuberculin type Hypersensitivity to Bacterial Allergen

Bacterial hypersensitivity also may be manifested by a more insidious and chronic process of which the tuberculin reaction is the prototype In tuberculin type hypersensitivities after a period of incubation diffuse pathological changes are encountered with principal involvement of collagen interstitial tissues and vascular endothelium of peripheral vessels endocardium and myocardium Resultant lesions are manifested in skin (urticaria purpura erythema etc) articular structures (arthralgia rheumatic fever rheumatoid arthritis etc) serous membranes (hydropericardium hydroperitoneum hydrothorax etc) kidneys (postscarlatinal nephritis) the nervous system (aseptic meningitis chorea nonsuppurative meningitides peripheral neuritis etc) endocardium (vegetations followed by scarring and valvular defects) myocardium (Aschoff bodies Anitschkow myocyte etc) and peripheral arteries (peri arteritis nodosa thrombo angiitis obliterans etc)

In tuberculin type hypersensitivity anaphylactic antibody is not demonstrable in circulating blood passive transfer cannot be demonstrated histamine injection does not reproduce the symptom complex antihistamines do not afford palliation but cortisone (Compound E) offers rich promise of effective symptomatic relief

Allergic Hypersensitivity Reactions to Bacterial Allergen vs Bacterial Inflammation

Clinically Bacterial Hypersensitivity and Bacterial Inflammation often are indistinguishable unless organisms are demonstrable in local lesions or in the blood stream Therapeutically antibiotics have curative potential in inflammatory reactions but additional sensitizing hazard in the allergies

When patients exhibit simultaneous manifestations of bacteremia toxemia and bacterial hypersensitivity differentiation is utterly impossible except through the therapeutic test of determining residual manifestations following effective antibiotic therapy When as in rheumatic

1 *Fastness* is bacteriologically selective applying to some but not all microbic strains

2 *Bacterial fastness* is also selective with regard to anti infective agents sulfonamide fast gonococci are penicillin sensitive many strep tomycin fast tubercle bacilli are dihydrostreptomycin sensitive and vice versa

3 The resistance of *fast bacterial strains* is relative and not abso lute Hence in acute infections the therapist is justified in the use of wastefully profligate loading or priming doses to overwhelm even the most stubborn invader

4 In chronic disease if the experience with streptomycin is generic there is a relationship between drug dose and active development of *bacterial immunity* Daily amounts in excess of 1 gm of streptomycin and courses of treatment extending beyond six weeks appear to invite fastness whereas a schedule which calls for 0 5 to 1 gm daily for forty two days seems to produce minimum microbic immunity without significant loss of therapeutic efficacy

5 There appears to be a direct relationship between development of *bacterial immunity* and *virulence* Patients whose organisms develop streptomycin resistance simultaneously experience clinical deteriora tion The appearance of *bacterial fastness* is prognostically ominous

6 *Fastness* is a property of the *microbe* not of the host Transmission of a streptomycin resistant tubercle bacillus from streptomycin treated patient to contact results in acquisition by the latter of a treatment resistant organism attesting to the grave menace of incomplete or uncontrolled therapy

Therapeutic Countermeasures The therapist has three potent meas ures with which to combat the antitherapeutic properties of acquired microbic re istance The first in the treatment of *acute* disease is the delivery of a massive and overpowering initial loading or priming dose precluding survival of even the hardiest subspecies of the bac terial invaders the second is substitution of another effective antibiotic agent as for example penicillin for sulfonamide dihydrostreptomycin for streptomycin and vice versa the third in *chronic* disease is the use of a time dose schedule devised to produce maximum therapeutic effect with minimum development of bacterial immunity

HYPERSENSITIVITY OF THE HOST TO BACTERIAL ANTIGEN

Bacterial and other invading micro organisms primarily damage the host by *actual invasion* (abscess carbuncle bacteremia etc) and/or by *toxin formation* and its release (diphtheria tetanus botulism etc)

Invasion of the Hypersensitive Individual Pathogens may cause tissue damage and death by acting as offending allergens in the manner of pollen in hay fever serum in anaphylactic shock strawberries in digestive urticaria milk and its products in infantile eczemas poison ivy in dermatitis venenata etc (p 3330)

Bacterial hypersensitivity just as other allergic phenomena may be manifested clinically as *acute histamine type* or *chronic tuberculin type* reactions elsewhere described in greater detail (p 4166) The

To the clinician the most alarming aspect of hypersensitivity is the possible injury he may unwittingly inflict on the patient whose tissues respond to introduction of the intended therapeutic agent by these perverse allergic manifestations Under these abnormal conditions an Unholy Alliance is established between invader and therapeutic agent The latter functions insidiously as a traitorous fifth columnist menacing the very patient whom the physician seeks to help

Histamine type Hypersensitivity Reactions to Therapeutic Agents

The clinician is abundantly familiar with both histamine type and tuberculin type hypersensitivity manifestations resulting from introduction of therapeutic allergens Thus an appreciable number of patients given serum or penicillin sooner or later develop a dermatosis (usually an urticaria) with or without drug fever and eosinophilia Usually there is little difficulty in recognizing the mechanism of these untoward manifestations which fortunately have only nuisance value and either abate spontaneously or respond to antihistamine

Tuberculin type Hypersensitivity Reactions to Therapeutic Agents

Until recently tuberculin type hypersensitivities to anti infective agents were not as obvious as histamine like responses The works of Rich and other investigators in this field have accentuated these basic precepts

1 Tuberculin type hypersensitivity (with many clinical features of peri-arteritis nodosa rheumatoid arthritis rheumatic fever etc) may be produced by injection of Heterologous Serum (p 4167)

2 Tuberculin type hypersensitivity may be produced by administration of nonprotein drugs such as iodide salicylate sulfonamide and presumably each and every anti infective agent

3 Treatment of bacterial hypersensitivity with potentially sensitizing anti infective agent may result in worsening of clinical manifestations and even death of host Thus anti infective agents prescribed or injected therapeutically may paradoxically prove damaging or even lethal to hypersensitive patients

The Combined Syndromes of Hypersensitivity Reactions Due to Bacterial and Therapeutic Allergens

In the presence of histamine type or tuberculin type hypersensitivities resulting from bacterial antigen the use of potentially sensitizing anti infective agents may produce the following complicated symptom complex always disturbing and occasionally lethal

a) Manifestations of microbic invasion and toxemia (fever leukocytosis bacteremia local inflammation etc)

b) Manifestations of histamine type hypersensitivity to Microbic Antigen (fever urticaria eosinophilia etc)

c) Manifestations of tuberculin type hypersensitivity to Microbic Antigen (sterile dermatoses endocarditis peripheral vascular lesions etc)

fever the phases of bacterial invasion and toxemia are terminated by the time the phase of bacterial hypersensitivity starts differential diag nosis is simpler and therapeutic indications are more precise

Therapeutic Implications

Present interpolation of the confusing topic of Bacterial Hypersensi tivity would be gratuitous were it not for the fact that recognition of microbic allergy is essential to intelligent conduct of therapy Succinctly stated the complication of hypersensitivity in any clinical syndrome resulting from or associated with bacterial invasion alters practical management in keeping with the following concepts

1 Antibiotic agents are of no value in controlling clinical manifes tations due to acute histamine type and chronic tuberculin type hyper sensitivity This principle is best illustrated by the disappointing results of sulfonamide and penicillin therapy in phase III of the rheumatic fever syndrome despite the etiologic relationship of the disease to an antibiotic sensitive organism (hemolytic streptococcus)

2 The patient who exhibits hypersensitivity to one antigen may exhibit hypersensitivity to others Hence introduction of an antibiotic agent exposes the hypersensitive patient to another potential allergen This in turn may produce additional hypersensitivity Illustrative of thi practitioners have long noted clinical deterioration in certain patients afflicted with deep fungus infections or tuberculosis when iodides were given and worsening of the rheumatic fever syndrome may follow use of sulfonamides (p 4179)

3 On the basis of negative therapeutic results and potential allergic damage antibiotics are not only not indicated in the treatment of clini cal manifestations due to bacterial hypersensitivity *they are actually contraindicated*

4 Once recognized manifestations of bacterial hypersensitivity merit treatment with antihistamines Histamine type manifestations should abate particularly if the bacterial invader has been eliminated and tuberculin type manifestations may be prevented Later when cortisone (Compound E) becomes available tuberculin type phenomena may be reversed as in rheumatoid arthritis

HYPERSENSITIVITY REACTIONS OF THE HOST TO DRUGS AND ANTIBIOTIC AGENTS

Attention has been previously drawn to these paradoxes

A Powerful antibiotics (penicillin streptomycin etc) may be derived from potentially invasive micro organisms (penicillium notatum actinomyces) (p 547)

B Perversions of mechanisms of defense may cause serious and even fatal consequences to the host (anaphylactic shock serum sick ness) (p 548)

Present attention is focused on a third and related paradox e g

C Exposure of the hypersensitive host to potent anti infective agents may result in histamine type or tuberculin type hypersensi tivities

of therapy weighing the potential hazard of hypersensitivity phenomena against possible anti infective responses

5 Concurrently with most anti infective agents *administer anti histamines* If this substance does nothing else it tends to prevent, or at least palliate manifestations of histamine type hypersensitivity whether due to bacterial antigen or to allergen derived from thera peutic agent.

6 In the management of any infection involving the *hypersensitive patient administer antihistamine prophylactically* hoping to ease if not prevent histamine type hypersensitivities and perhaps lessen the tendency to later development of tuberculin type hypersensitivity

7 In the management of any disease caused by *microbes of high ensitizing potential* (streptococci M tuberculosis etc) *give anti histamine to prevent or palliate histamine type hypersensitivities* and perhaps later *tuberculin type hypersensitivities*

8 *Continue administration of antihistamine for at least two weeks after potentially sensitizing antigens have been eliminated* (discon tinuance of anti infective agent abatement of microbic activity)

9 In intervals of respite (as Phase II of the rheumatic fever syn drome) *attempt to prevent exacerbations by systematic use of a feebly sensitizing but powerfully bactericidal anti infective agent* (penicillin) *together with antihistamine*

10 When commercially available consider use of anterior pituitary adrenocorticotropic hormone or of cortisone to palliate and perhaps prevent chronic tuberculin type hypersensitivity reactions

INCREASED COAGULABILITY OF THE BLOOD

The blood of patients receiving penicillin streptomycin and aureo mycin clots more rapidly than normally Thus within 75 minutes after oral administration of aureomycin the coagulation time of cats is reduced from eleven minutes to four minutes A single capsule contain ing 250 mg of aureomycin reduces the coagulation time of human blood from eight to five minutes

Practical application of this antitherapeutic effect of the antibiotic is seen in the increase in the complications of phlebothrombosis and embolization when penicillin and aureomycin particularly are used for the prevention or active treatment of postoperative infection Par ticularly in known thrombophiles (p 4571) the practitioner must consider the hazard of antibiotic and weigh this factor against potential benefits If it is decided that antibiotic is to be administered then early ambulation is the more urgently required in order to prevent serious intravascular complications and difficulties

SUMMARY

In the fascinating biological conflict between human host and hostile microbic foe the battle lines are drawn according to the following schematic pattern

d) Manifestations of histamine type hypersensitivity to Therapeutic Allergen (fever dermatoses eosinophilia etc)

e) Manifestations of tuberculin type hypersensitivity to Therapeutic Allergen (toxicoderms vascular lesions resembling periarteritis and endocarditis sterile effusions etc)

Confirmation of these experimental data is afforded clinically by observed deterioration in rheumatic fever on prescription of sulfona mide by the flare up that may occur when iodide is administered to certain patients with tuberculosis and deep fungous infections by ten fold increase in the incidence of a fatal peri arteritis nodosa at the Johns Hopkins Hospital in the decade following introduction of sulfonamide therapy (p 4179)

Therapeutic Implications

In the light of modern knowledge bacterial and therapeutic sensi tivity *reactions have a great deal more than academic significance* Unless clearly assessed at their proper valuations bacterial hypersensi tivities (particularly of the tuberculin type varieties) may produce crip pling and even fatal disturbances The therapist who fails to compre hend the pathogenesis of the condition under consideration may add fuel to the fire by superimposing hypersensitivity phenomena resulting from his prescription of suppo edly therapeutic agents as for example *sulfonamides in rheumatic fever* Contrariwise the astute and com pleat practitioner with keen awareness of the complexity of bacterial invasion and of mechanisms of therapeusis supplements the miracles of anti infective therapy with measures aimed to prevent and palliate hypersensitivity phenomena whether caused by invading micro organi m or potential anti infective therapeutic agent

Until such time as there is available greater knowledge of hyper sensitivity the undernoted *guiding principles* are recommended for serious consideration

1 In the treatment of infection when the invading microbe is sus ceptible to several antibiotics *choose an anti infective agent of feebly sensitizing potential* (penicillin) rather than one of seemingly greater sensitizing potential (sulfonamide)

2 In the treatment of infections e pecially in hypersensitive patients *avoid anti infective agents of feeble or dubious antimicrobic activity* especially if these substances are potentially sensitizing antigens (iodide salicylate gold etc)

3 If the patient gives a personal or family history of hypersensitivity (hay fever dermatitis venenata from poison ivy hives from digestants asthma etc) of previous hypersensitivity to anti infective agents (drug fever toxicoderm serum sickness etc) and if there are objec tive evidences of *hypersensitivity phenomena* (*eczema purpura erythema* etc) *weigh the potential hazard of hypersensitization to the therapeutic agent against its possible anti infective capacity*

4 *If the patient develops evidences of hypersensitivity* to the thera peutic agent during anti infective treatment *consider discontinuance*

of therapy weighing the potential hazard of hypersensitivity phenomena against possible anti infective responses

5 Concurrently with most anti infective agents *administer anti histamines* If this substance does nothing else it tends to prevent or at least palliate manifestations of histamine type hypersensitivity whether due to bacterial antigen or to allergen derived from thera peutic agent

6 In the management of any infection involving the *hypersensitive patient administer antihistamine prophylactically* hoping to ease if not prevent histamine type hypersensitivities and perhaps lessen the tendency to later development of tuberculin type hypersensitivity

7 In the management of any disea e caused by *microbes of high ensitizing potential* (streptococci M tuberculosis etc) *give anti histamine to prevent or palliate histamine type hypersensitivities* and perhaps later *tuberculin type hypersensitivities*

8 *Continue administration of antihistamine for at least two weeks after potentially sensitizing antigens have been eliminated* (discon tinuance of anti infective agent abatement of microbic activity)

9 In intervals of respite (as Phase II of the rheumatic fever syn drome) *attempt to prevent exacerbations by systematic use of a feebly sensitizing but powerfully bactericidal anti infective agent* (penicillin) *together with antihistamine*

10 When commercially available consider use of anterior pituitary adrenocorticotropic hormone or of cortisone to palliate and perhaps prevent chronic tuberculin type hypersensitivity reactions

INCREASED COAGULABILITY OF THE BLOOD

The blood of patients receiving penicillin streptomycin and aureo mycin clots more rapidly than normally Thus within 75 minutes after oral administration of aureomycin the coagulation time of cats is reduced from eleven minutes to four minutes A single capsule contain ing 250 mg of aureomycin reduces the coagulation time of human blood from eight to five minutes

Practical application of this antitherapeutic effect of the antibiotic is seen in the increa e in the complications of phlebothrombosis and embolization when penicillin and aureomycin particularly are used for the prevention or active treatment of postoperative infection Par ticularly in known thrombophiles (p 4571) the practitioner must consider the hazard of antibiotic and weigh this factor against potential benefits If it is decided that antibiotic is to be administered then early ambulation is the more urgently required in order to prevent serious intrava cular complications and difficultie

SUMMARY

In the fascinating biological conflict between human host and ho tile microbic foe the battle lines are drawn according to the following schematic pattern

Host	*Microbic Invader*
Natural Active Immunity (p 76)	Bacterial Body
+	+
Natural Passive Immunity (p 73)	Bacterial Toxin
+	+
Artificial Active Immunity (p 75)	Bacterial Fastness (Microbic Immunity)
+	+
Artificial Passive Immunity (p 75)	Hypersensitivity to Microbic Antigen
+	+
Antibiotic Agents	Hypersensitivity to Therapeutic Allergen

The e then are the pieces in what may be a game of mortal conflict Each factor is an imponderable for as yet medicine has no laboratory yardstick by which to measure the power of each constituent The *apotheosis of the art of medicine is best exhibited in the practitioner s* interpretation of presenting symptoms and in the manner in which he utilizes the varied therapeutic modalities to overcome the microbic invader and suppre s or minimize antitherapeutic hazards

ACTINOMYCOSIS

[Lumpy Jaw Nocardiosis Streptothricosis]

Principles of Diagnosis and Treatment

1 Establish diagnosis by spreads or cultures (Fig 75A p 486 and p 492)

2 Inasmuch as actinomycosis is a relatively rare disea e few writers have sufficiently exten ive experience to speak authoritatively of thera peutic endeavors The practitioner treating an occasional infection proceeds tentatively carefully observes effects of therapy prepares to make changes if indicated and seeks consultation with specialists when necessary

3 Remember that actinomycosis is an insidious disease (p 489) hence treatment must be vigorous and sustained Even when the pri mary lesion appears sharply localized (Fig 965 p 3310) latent pul monary (Fig 77 p 491) and abdominal metastases later may produce chronic illness and/or death

4 Actinomyces vary greatly in susceptibility to antibiotics Most strains exhibit some ensitivity to penicillin sulfonamides and the strep tomycins To be effectual anti infective therapy must be pursued inten sively with combinations of several available agencies

Practical Management

Immediate Care

1 Arrange for admission to a ho pital equipped to handle communi cable disease unle s patient can be i olated at home under professional nursing supervision Warn attendants of infectivity of dres ings and sputum

2 In addition to routine physical and laboratory examinations x ray chest to detect current le ions and for comparison with later films

3 Order high calory diet (p 671) with multivitamin supplementation

4 Consider surgical extirpation and curettement preferably under general anesthesia if primary lesion can be excised without significant disability or disfigurement

5 Contact National Institute of Health Bethesda Maryland for acti nomycosis vaccine not commercially available When obtained inject intracutaneously 0 1 cc for test of skin sensitivity Read at 24 and 48 hours Interpret as positive an area of erythema in excess of 2 cm In the hypersensitive defer use of iodide or irradiation until desensiti zation has been accomplished (p 4190)

6 Inject intramu cularly a priming dose of at least 1 200 000 units of procaine penicillin in aqueous suspension (p 4453)

7 Administer orally 2 gm each of sulfadiazine and sulfamerazine

Host	*Microbic Invader*
Natural Active Immunity (p 76)	Bacterial Body
+	+
Natural Passive Immunity (p 73)	Bacterial Toxin
+	+
Artificial Active Immunity (p 75)	Bacterial Fastness (Microbic Immunity)
+	+
Artificial Passive Immunity (p 75)	Hypersensitivity to Microbic Antigen
+	+
Antibiotic Agents	Hypersensitivity to Therapeutic Allergen

These then are the pieces in what may be a game of mortal conflict Each factor is an imponderable for as yet medicine has no laboratory yardstick by which to measure the power of each constituent The apotheosis of the art of medicine is best exhibited in the practitioner s interpretation of presenting symptoms and in the manner in which he utilizes the varied therapeutic modalities to overcome the microbic invader and suppress or minimize antitherapeutic hazards

8 If iodide is not tolerated o ally substitute inhalations of ethyl iodide using apparatus of Burnham or Warren Collens (p 4378) Start with 0 2 cc thrice daily Increase by increments of 0 1 cc until full dose of 1 cc is tolerated

Continuing Care (Progressively Unfavorable Course)

1 Maintain or increase penicillin levels by use of larger doses of aqueous procaine penicillin G or by substitution of su pension in oil with aluminum monostearate

2 Increase streptomycin to 1 gm thrice daily

3 Continue antihistamine vaccine and aerosolization

4 Substitute sulfones for sulfonamides Start with promizole as in leprosy (p 4386) with initial daily dose of 0 5 gm in capsule form Increase daily dose by increments of 0 5 gm to total 6 to 8 gm daily closely watching hemogram Inject daily 1 cc of liver extract Group and cross match for transfusion if erythrocytes fall below 3 000 000 or hemoglobin is less than 7 5 gm

5 Substitute diasone for promizole Give 0 9 gm daily for first week Increase daily dose to 1 2 gm for second week and to 1 5 gm there after unle s toxicity is encountered (p 4552) Interrupt diasone therapy for two weeks every two months

6 If sulfones appear ineffectual or toxic try thymol Start with 300 mg thrice daily Add 300 mg each day if tolerated (p 4586) to daily total dose of 2 1 gm

7 Consult surgeon for radical operative intervention Consider (a) excision of sinus tract (b) lobectomy if pulmonary lesions are local ized (c) laparotomy for drainage of peritoneal absce s etc

ADRENAL CORTICAL EXTRACTS AND ANTERIOR PITUITARY ADRENOCORTICOTROPIC HORMONE [ACTH]

Until the monumental clinical researches of Philip Hench interest in adrenal cortical extracts and anterior pituitary adrenocorticotropic hor mone centered on substitution therapy in hypopituitarism (pp 1164–1174) and Addisonian adrenal cortical insufficiency (p 1271) With Hench s demonstration of the potential of artificially induced hyper cortinism fields of investigation broadened to include inquiries into the pathogenesis and treatment of many syndromes previously imper fectly understood and therapeutically resistant Already there is rich promise of incalculable benefits on the realistic plane of patient man agement and on broader biologic levels it becomes possible to inte grate the seemingly unrelated di ciplines of endocrinology immunology allergy infection and neoplastic disease

Attempts to summarize such active fields of investigation involve difficulties and hazards Nevertheless the following collection and clas sification of available information (derived from recent current and

with 4 gm of sodium bicarbonate If patient is desperately ill or nauseated substitute intravenous injection of 2 5 gm each of sodium sulfadiazine and sodium sulfamerazine in 200 to 500 cc of sterile diluent preferably molar lactate

Continuing Care (Favorable Course)

1 Maintain penicillin levels for minimum period of two months with two daily injections each of 300 000 units of procaine penicillin G in aqueous suspension If daily injections are inconvenient substitute (a) 250 000 units of penicillin G orally three times daily between injections or (b) deposit 300 000 to 600 000 units of procaine penicillin G in oil with 2% aluminum monostearate for 48 to 96 hour levels

2 With signs of pulmonary involvement supplement parenteral penicillin with aerosolizations twice or thrice daily using additional 100 000 units of penicillin G for each treatment

3 Maintain sulfonamide levels for two or three weeks provided there are no evidences of toxicity (p 94) Use oral doses of 0 5 to 1 gm each of sulfadiazine and sulfamerazine thrice daily

4 Concurrently with penicillin sulfonamide give antihistamine prophylactically Prescribe 50 mg of pyribenzamine or benadryl four times daily

5 After skin sensitivity has been determined initiate vaccine therapy Start sensitized patient with 0 1 cc of 1 100 or 1 1000 solution depending on degree of erythema Non sensitive may be given 0 1 cc of undiluted vaccine Give injections every second or third day increasing dose by increments of 0 1 cc if possible until full dose of 1 cc of undiluted vaccine is tolerated

6 If the wound has been surgically treated irrigate several times daily with aqueous penicillin G (1 cc = 10 000 units)

Continuing Care (Unfavorable Course)

1 Increase penicillin levels by raising daily doses as high as 10 000 000 units of aqueous procaine penicillin G

2 Unless there are manifestations of sulfonamide toxicity step up daily dose to 6 to 9 gm Get daily hemogram and urine for evidences of blood dyscrasia and/or renal irritation

3 Supplement penicillin sulfonamide combination with intramuscular injections twice daily of 1 gm streptomycin

4 Add 0 5 gm streptomycin to penicillin aerosol

5 Continue antihistamine and vaccine

6 If primary lesion has not been excised and patient is not skin sensitive consider roentgen therapy If patient is skin sensitive postpone irradiation until undiluted vaccine is tolerated

7 If primary lesion has been excised and radiation therapy cannot be given for whatever reason initiate iodide therapy Start with 0 6 to 1 cc of saturated potassium iodide thrice daily in milk or soup Increase total daily dose by increments of 0 2 cc to maximum daily dose of 12 cc unless manifestations of iodism (p 612) are encountered

ADRENAL CORTICAL PREPARATIONS AND SUBSTITUTES (*Continued*)

Preparation	Comment
	dosage may cause hypertension, cardiac hypertrophy and edema For production of therapeutic hypercortinism inject 5–10 mg intramuscularly followed, within 5 minutes by intravenous introduction of 100 mg of ascorbic acid Do not persist unless prompt alleviation of symptoms is noted.
Desoxycorticosterone Pellets (Schering Ciba)	For subcutaneous deposit in maintenance of remission in Addisonian adrenal cortical insufficiency Use 100 mg equivalent to daily doses of 0 3–0 4 mg of peanut oil preparation.
DOCA (Roche)	See Desoxycorticosterone Acetate
Estrogen	Suggested substitute for cortone in the production of artificial therapeutic hypercortinism May have possibilities in the management of male schizophrenics
Lipo Adrenal Cortex (Upjohn) N N R.	Oil soluble extract of whole gland containing 17 hydroxycorticosterone 11-dehydro-17 hydrocorticosterone and 11-dehydrocorticosterone For substitution therapy in Addisonian adrenal cortical deficiency inject intramuscularly 2–5 cc every 6–8 hours So far as is presently known ineffective in the production of artificial therapeutic hypercortinism
Percorten (Ciba) N N R.	See Desoxycorticosterone Acetate
Δ-5 pregnenolone (Prenolon Schering)	Suggested substitute for cortone in the production of artificial therapeutic hypercortinism Give intramuscularly in daily doses of 100–200 mg (Davison et al Arch Int Med 85 365)
Prenolon (Schering)	See Δ 5 pregnenolone
Testosterone Propionate	Suggested substitute for cortone in the production of artificial therapeutic hypercortinism May have possibilities in the management of female schizophrenics

CORTONE (MERCK) CORTISONE ACETATE, COMPOUND E (KENDALL)

Cortone acetate is chemically 11 dehydro 17 hydroxy corticosterone 21 acetate It is identical with compound E of Kendall Substance FA (Reichstein) and compound F (Wintersteiner and Pfiffner) Cortone is also referred to in the literature as cortisone and as cortisone acetate

Cortone has been synthesized from bile acids in the Merck Laboratories by L H Sarett It is a white or nearly white powder oluble in water to the extent of 2 mg per 100 cc For clinical use it is marketed in saline solution with inert suspending agents and 1 5 per cent benzyl alcohol as a pre ervative At room temperature cortone decomposes very slowly However the product must not be refrigerated lest the suspension alter its physical state and become decreased in its efficacy

Currently cortone acetate is supplied in vials containing 12 cc or the equivalent of 300 mg Thus each single cc possesses the activity of 25 mg of cortone acetate when injected intramuscularly through a

pending researches) particularly highlight those reports which po sess therapeutic possibilities in medical practice Additionally there are included tentative suggestions for the treatment of conditions in which there are theoretical possibilities at least for symptomatic relief For more complete details and bibliographic references the reader is urged to consult Dr Hench s collective abstract in the Archives of Internal Medicine 85 545 (April 1950) and the Proceedings of the First Clinical ACTH Conference edited by Dr John R Mote (Blakiston Company 1950)

ADRENAL CORTICAL EXTRACTS

Prime interest in adrenal cortical extracts previously focussed on desoxycorticosterone used specifically in the treatment of Addisonian adrenal cortical deficiency Currently attention is directed to 17 hydroxy 11 dehydrocorticosterone known also as compound E corti sone and cortone (Merck) whose remarkable clinical effects are not duplicated by any other of the listed products yielded by the adrenal cortex

ADRENAL CORTICAL PREPARATIONS AND SUBSTITUTES

Preparation	Comment
Adrenal Cortical Extract (Parke Davis and Upjohn) N N R	Aqueous extract of gland freed from epinephrine Assayed so that 1 cc = 50 units (Cartland Kuzenga) For Addisonian crises inject intramuscularly or intravenously 20 cc (1 000 units) Repeat every 2 or 3 hours as needed For maintenance 500 units daily may suffice
Arti one (Wyeth)	Commercially available brand of pregnenolone
Compound A (11-dehydrocorti co terone)	Not commercially available Apparently ineffective for substitution therapy or for production of artificial hypercortini m
Compound E (Cortisone Cortone Merck) (17 hydroxy 11 dehy drocorticosterone)	Currently the most effective product for production of artificial therapeutic hypercortinism Used in symp tomatic treatment of a diversity of clinical disorders including histamine type and tuberculin type hyper sensitivities bacterial and other allergies neoplasms etc Commercially available to a limited degree as cortone (Merck) See accompanying descriptive material (p 4145)
Compound F (17 hydroxycorti costerone)	Not commercially available Has some of the thera peutic properties of compound E but to a con siderably lesser degree
Cortisone	See compound E
Cortone (Merck)	See text (p 4145)
Desoxycorticosterone Acetate (Doca Roche Percorten Ciba) N N R	Peanut oil solution of ynthetic steroid prepared so that 1 cc = 5 mg For Addisonian crisi inject intra muscularly 5-10 mg For maintenance give 1-5 mg together with 6-8 gm of sodium chloride Over

Specific Substitution Therapy with ACTH

Within certain well defined limitations ACTH holds promise for sub stitution treatment in hypopituitarism and al o in Addisonian adreno cortical deficiency

In the hypopituitary states of dwarfism (p 1164) mongolian idiocy (Fig 243 p 1166) Laurence Moon Biedl syndrome (p 1166) Frohlich adiposo-genital syndrome (Fig 244 p 1168) and Simmonds di ease (Fig 245 p 1171) a trial of injections is certainly warranted However sensational results cannot be anticipated since anterior pituitary adreno-corticotropic hormone contains neither growth follicle stimulating luteinizing gonadotropic thyrotropic nor lactogenic principles of pan pituitary secretion

In the treatment of Addisonian adrenocortical deficiency ACTH should prove superior to cortone since it evokes the *outpouring* of all adrenal cortical principles whereas adrenocortical extract merely *sup plies* 11 dehydro-17 hydroxycorticosterone Against the advantage of provision of pan adrenocortical ecretion is the off et that the handi capped hormonal structure must contain sufficient viable tissue to re pond to stimulus from the master gland if the patient is to benefit from injections In all likelihood optimum therapeutic results will be obtained by combining timulation by ACTH and substitution with cortone

THE EVOLUTION OF THE CONCEPT OF ARTIFICIALLY INDUCED THERAPEUTIC HYPERCORTINISM

The therapeutic potential of artificially induced hypercortinism was first recognized and eventually demonstrated by Philip Hench in a eries of researches which rank with the greate t of medical triumphs In order fully to appreciate Hench s monumental contributions the reader is urged to familiarize himself with the material on Allergy in this current Progress Volume (p 4163) and with the Introduction especially tho e subdivisions concerned with histamine type and tuber culin type hyper ensitivity reactions

When the concept of hypersensitivity reactions has been clearly understood intelligent use of ACTH and cortone will be enhanced by tracing the steps which led Hench from nebulous hypothesis to defini tive therapeutic triumph

1925

1 From the observation that weaknes fatigue and hypotension were commonly observed in patients with rheumatoid arthritis Hench pre dicated that in connection with or in addition to a suppo ed factor of infection secondary metabolic changes were present and that these latter somehow involved the adrenal glands

2 Post mortem examination of adrenal glands of two patient who had suffered from rheumatoid arthritis afforded no support to the hypothesis

20 gauge or larger hypodermic needle The average daily dose of cortone approximates 100–200 mg Optimum dosage depends on patient response

ANTERIOR PITUITARY ADRENOCORTICOTROPIC HORMONE [ACTH]

Adrenocorticotropic principle was first isolated by Collip in 1933 *Further purification was accomplished by a variety of workers* resulting in the isolation of a protein complex with a molecular weight approximating 22 000 In 1948 Li disintegrated ACTH by pepsin digestion into a mixture of smaller units Of these a peptide fragment of low molecular weight was discovered to retain the adrenal stimulating properties of whole ACTH protein

Only small quantities of ACTH have been recovered since its first isolation Until February 8 1949 when ACTH first was injected by Hench as a substitute for compound E in the treatment of rheumatoid arthritis available supplies were used for physiologic studies and for treatment of Addison s disease various hypopituitary states and miscellaneous syndromes

Currently ACTH is not commercially available The limited supplies prepared by the Armour and Wilson Laboratories from pituitary glands of hogs are allocated to qualified research workers by the director Dr John R Mote to whom application must be made The present preparation of ACTH is a saline solution containing a small amount of impurity consisting mostly of posterior pituitary substance and some pigment producing pars media secretion Injections are made intramuscularly in average daily doses of 100 mg pharmacologically equivalent to approximately 200 mg or more of cortone Since ACTH is utilized rapidly by the body the total daily dose is best given in divided amounts at 6 to 8 hour intervals

None of the previously described commercially available preparations of anterior pituitary extracts (Table 79 p 1154) possesses significant adrenocorticotropic activity Hence they cannot be substituted effectually for ACTH Conversely ACTH is devoid of significant growth lactogenic follicle stimulating luteinizing gonadotropic and thyrotropic principles Therefore ACTH must not be regarded as a pan pituitary product

Specific Substitution Therapy with Cortone

Most manifestations of Addisonian adrenal cortical deficiency are controlled by remarkably small doses of cortone However since cortone is but one of many principles secreted by its parent gland maintenance of normal blood electrolyte levels and complete dissipation of symptomatology require supplementary administration of desoxycorticosterone and sodium chloride (p 4160)

Whereas ACTH also may be used in the treatment of Addison s *disease* cortone is of no value in the management of hypopituitarism since the anterior pituitary adrenocortical interrelationship is not reversible and proceeds exclusively from the former to the latter

cortin was administered to three patients with rheumatoid arthritis but the results were unimpressive

1942

Having neither compound E nor any other potent adrenal product Hench decided to induce jaundice in arthritic volunteers by introduction of lactophenin Temporary remissions were induced but the agent responsible for improvement could not be identified

May 1948

During the years of Hench s persistent devotion to his problem (1925-1948) prodigious cooperative efforts were being made to produce compound E by Kendall and his associates at the Mayo Clinic and by Dr L H Sarett of Merck and Company Until May 1948 only enough material was obtained for treatment of a few patients with Addison s disease whose lives were in jeopardy

Sept 21 1948

1 On September 21 1948 Merck and Company made available for the treatment of one woman badly crippled with rheumatoid arthritis (Case 1 Arch Int Med 85 613) a small supply of compound E This was administered as the very first clinical trial of a hypothesis that had emerged as the result of twenty three years of study observation and experimentation The results of this historic event are best told in Hench s own words

On the morning of September 21 before the first injection of cortisone the patient could hardly get out of bed once she tried to walk it was too painful and so she remained at rest But on September 23 after two days of use of cortisone she woke with much less muscular stiffness and soreness rolled over in bed easily for the first time in weeks and noted increased strength and appetite Although she felt much better subjectively and the fibrositic component seemed to be much decreased articular tenderness was unchanged On the next day (September 24) improvement continued and we found her exercising raising her hands over her head previously impossible She visited several patients to demonstrate her changed condition Painful stiffness was gone My muscles feel stronger and my appetite is very good After six days of use of cortisone she had lost almost all her stiffness articular tenderness and pain on motion were markedly reduced The next afternoon (September 28) she shopped for three hours downtown feeling tired thereafter but not sore or stiff She noted a sense of well being I have never felt better in my life

2 When we noted in September 1948 the effect of cortisone on rheumatoid arthritis it seemed logical to determine as soon as possible the effect of ACTH also since ACTH stimulates response of adrenal glands to produce cortisone or the cortisone like substance compound F Before giving it we were not certain what our results would be If the adrenal glands of rheumatoid patients were producing

1929

1 Failing to establish a morphologic relationship between adrenal glands and rheumatoid arthritis Hench noted (as had many before him) an amelioration of manifestations of rheumatoid arthritis as the result of coincidental jaundice Contrary to current opinions he concluded that rheumatoid arthritis was potentially reversible It was not necessarily a relentlessly progressive uncontrollable disease for which no really satisfactory and rapid treatment or control need ever be expected

2 Hench suggested the label anti rheumatic substance X for the unknown ameliorating agent which he then believed to be an hepatic or biliary constituent

3 Trials using hepatic substances in the treatment of rheumatoid arthritis were conducted without success

1931

From the clinical observation that pregnancy also exerts a beneficial effect on rheumatoid arthritis Hench questioned whether the agents responsible for relief by pregnancy and jaundice were identical or closely related

1938

1 When he noted that jaundiced rheumatoid men experienced the same relief as pregnant non jaundiced rheumatoid women Hench concluded that so called anti rheumatic substance X could be neither bilirubin nor female sex hormone He suggested that it was probably a biologic compound specific in nature and function and normal in healthy human organisms but perhaps lacking or deficient in patients with rheumatoid arthritis

2 Since pregnancy alters the concentration of hormones and disturbs hormonal equilibrium the suspicion arose that anti rheumatic substance X might be a bisexual steroid hormone Among substances that Hench listed for eventual trial in testing his hypothesis was whole adrenal cortex extract then called cortin

Following the observation that pregnancy and/or jaundice not only relieved rheumatoid arthritis but sometimes behaved equally favorably in non rheumatic conditions (hay fever asthma egg sensitivity migraine and psoriasis) Hench suggested that the phenomenon of relief was not specific to rheumatoid arthritis but was rather group specific With uncanny prescience the investigator now suspected that anti rheumatic substance X if identified would find usefulness in the management of a number of disturbances

1941

1 During conferences with Kendall a note was made to try compound E when it became available Unfortunately there was no preparation at that time suitable for injection into the human being

2 In the absence of compound E Kendall s adrenal cortical extract

festations of a perver e response to trauma clinically desirable phenomena are observed in the antirheumatic effects of diminution in synovial and articular swelling reduction of pyrexia tachycardia and erythrocyte sedimentation rates and abolition of pain Yet if it becomes necessary to perform surgical procedures during the course of artificially induced hypercortinism the wound will not heal and fractures incidentally suffered will fail to unite Conversely if during the course of incidental operative procedure or traumatic experience administration of cortisone and/or ACTH is discontinued the wound of the normal skin will heal and the fracture will unite but the manifesta tions of the perverse respon e clinically recognizable as the syn drome of rheumatoid arthritis will recur

There is about the results of artificially induced hypercortinism none of the relative certainty that prevails for example in penicillin treat ment of gonorrhea Of Hench s first series of twenty three patients with rheumatoid arthritis treated with cortisone or ACTH nine experienced marked antirheumatic effects with no or minimal side effects eight had marked antirheumatic effects but mild side effects two had marked antirheumatic effect and moderate side effects and four had marked or moderate antirheumatic effects and marked side effects Following withdrawal of cortisone or ACTH some patients experienced an imme diate return of rheumatic activity others suffered a rebound relapse in which their condition was wor e than it was before treatment still others had reasonably protracted relief and the most fortunate experi enced longer remissions that have lasted up to a year at the time of Hench s publication

These clinical vagaries of artificially induced hypercortinism have not been emphasized for the purpose of discouraging the practitioner from use of cortone and/or ACTH nor are they intended to support the views of academicians who insist that institutionalization is required for this type of hormonal therapy They are pre ented to alert the *practitioner to the necessity for careful observation and thoughtful* interpretation during the course of his clinical experiment It is only by thorough knowledge of the potentialities of hypercortinism that the therapist can have any appreciation of seemingly paradoxical responses and of individual variations

Cortone and ACTH are as easily injected as insulin Undesirable effects are readily recognizable by the careful clinician who observes conscientiously the course of therapy Undesirable manifestations are transitory and usually are reversible as soon as hormonal disequili brium is corrected by interruption of glandular therapy For more enlightened guidance the accompanying charts have been prepared to demonstrate the wide range of manifestations due to clinically induced hypercortinism and the many variables often dependent on imponderable individual circumstances

EFFECTS OF ARTIFICIAL HYPERCORTINISM

Adipose Tissue

Rounding of face increased width of pelvic girdle and development of retro cervical fat (buffalo hump) as in Cu hing s hyperadrenalinism Noted in approximately 30% of patients particularly those under long term therapy

not cortisone but an altered product related to the causation of the disease stimulation of such adrenal glands might increase rather than decrease articular symptoms

Feb 8 1949

ACTH was given (case 14) 100 mg daily (25 mg at 8 A M and 4 P M and 50 mg at 10 P M) for 12 days (Feb 8–19) Within about a week stiffness had disappeared and tenderness and aching were decreased After 11 days of use of ACTH the patient had complete subjective relief an estimated over all relief of 90 per cent She had three consecutive days free of pain the first such in five years The sedimentation rate fell precipitously 75 mm during the first *9 days on ACTH from 93 to 18 mm*

Clinical Manifestations of Artificially Induced Hypercortinism

Deliberate induction of hypercortinism for therapeutic purpose is a clinical experiment involving so many imponderables that prediction of anticipated results is a hazardous undertaking even for the experienced As Hench has stated Cortisone and ACTH are potent agents capable of affecting many parts of the human economy many bodily functions and many tissues other than those of joints and muscle

Under certain circumstances some effects of hypercortinism are desirable while others may be decidedly undesirable The diabetic with rheumatoid arthritis simultaneously may experience a favorable antirheumatic response in association with diminished carbohydrate tolerance and increased insulin resistance The rheumatic child on the verge of backward failure may be relieved of arthralgia and pyrexia yet suffer sufficient water retention to be thrown into pulmonary edema In each instance both desirable and undesirable manifestations are equally explicable results of the artificially disturbed hormonal equilibrium It is not correct to state that desirable features are clinical effects and that undesirable are side or toxic effects Each as Hench insists is an understandably physiologic response to the administration of potent adrenocortical hormone or adrenocorticotropic factor

Among immeasurable variables which may determine responses to artificially induced hypercortinism are prevailing endocrinal equilibriums and the existing functional state of terminal tissues Illustrative of the former Selye has shown an antagonistic relationship between the intrinsic adrenal cortical secretions desoxycorticosterone and cortisone Injections of the former produce much more significant hypertensive effects in adrenalectomized than in normal animals suggesting that intact gland secretes a substance (probably cortisone) antagonistic to pressor effects of desoxycorticosterone

Again manifestations of artificially induced hypercortinism may depend on the functional state of end tissues at the time of production of glandular disequilibrium Normal epidermal and mesenchymal structures respond to hypercortinism by sluggish or absent responses to injury In the patient with rheumatoid arthritis suffering from mani

Eosinophils Circulating

No consistent change with cortone but specific eosinopenia from effective doses of ACTH Use total eosinophile count as guide to therapy Greatest degree of eosinopenia occurs 3-5 hours after intramuscular injection of an adequate dose of ACTH Reduction of eosinophils below 100 cells per cu mm often associated with overdosage phenomena Failure of eosinopenic response usually indicates clinically inadequate therapeutic response (Mote p 6)

Epithelium

Growth inhibited Lack of epithelialization delays wound healing but exerts a favorable effect in psoriasis and other dermatoses probably related to tuberculin type hypersensitivity (p 4169)

Erythrocytes Circulating

Tend to rise when hypercortinism is induced in conditions associated with anemia

Erythrocyte Sedimentation Rate

Tends to fall when hypercortinism is induced in conditions associated with rapid rates

Fibrin and Fibroblasts

Depression delays wound healing in normal areas but favors antirheumatic effects on synovia articular structures and subcutaneous nodules

Flexion Deformities

Rapidly disappear if due to non fibrous lesions secondary to hypersensitivity phenomena

Granulations

Inhibition delays wound healing but favors antirheumatic effects

Hair

Hirsuties presumably due to increased androgenic activity Particularly undesirable in females

Heart Rate

Tachycardia rapidly diminishes if increased pulse rate is due to hypersensitivity manifestations

Hemoglobin

Tends to rise when hypercortinism is induced in conditions associated with anemia

Leukocytes Circulating

Occasional increase in total numbers of circulating leukocytes and immature granulocytes with eosinopenia and lymphopenia Latter effect utilized in treatment of lymphatic leukemias malignant lymphomas follicular lymphoblastoma etc

Libido and Potentia

Diminished in 3 of 8 men

Lymph

Depression favors decrease of swelling as part of antirheumatic effect

Lymphocytes Tissue and Plasma Cells

Inhibition delays wound healing in normal structures but may favor antirheumatic effects

EFFECTS OF ARTIFICIAL HYPERCORTINISM (*Continued*)

Anaphylatoxin

Production inhibited sugge ting that patient with artificially induced hyper cortinism has greater re istance to anaphylactic hock and other hypersen i tivity reactions including serum ickness May prove future aid to prophylaxis and active treatment of acute hi tamine type hypersen itivity reactions

Antibody Circulating

Titers significantly decreased resulting in increased vulnerability of patient to bacterial invasion. Practical suggestions include need for massive doses of indicated antibiotic and/or temporary intermi sion of cortisone or ACTH until infection is controlled

Appetite

Increases strikingly with loss of symptoms due to hypersensitivity phenomena

Arthropathies

Rapidly ameliorated if due to perversion of the mechanisms of bodily defense (rheumatoid arthritis rheumatic fever etc)

Blood Coagulability

Blood sludging ignificantly decrea ed Possible future application of this ob ervation to prevention and treatment of intravascular clotting in throm bophiles (p 4571)

Blood Pressure

No significant consistent changes Cortone may offset hypertensive effects of desoxycorticosterone

Body Temperature

Tends to revert to normal when fever is due to conditions amenable to arti ficial hypercortinism (Rheumatic fever rheumatoid arthriti disseminated acute lupus erythematosu peri arteritis nodosa etc)

Callus (in Fractures)

Formation inhibited in experimentally produced lesions of cortone treated animals

Capillary Tufts

Depre sion delays granulation of artificially induced wounds in normals but may favor antirheumatic effects

Carbohydrate

Under normal condition but slight impairment of carbohydrate tolerance With very large doses of cortone or ACTH marked hyperglycemia with glycosuria In the treatment of rheumatic patients with as ociated or coin cidental diabetes mellitus there may be marked reduction of carbohydrate tolerance with increased insulin resistance suggesting an adrenocortical hyperglycemia

Corticosteroids

Urinary concentration initially increased during artificial hypercortinism. After long-continued admini tration levels fall suggesting exhau tion of the glandular mechani m and exposing the patient to les ened responses to emergency demands incidental to acute infections or indicated surgery

Elastic Tissue

Friability results in reddish striae particularly over thighs Most often seen in young girls under therapy

Weight

Nutritional gains with increased appetite and diminution of symptoms resulting from hypersensitivity phenomena Rapid and transitory gains more likely the result of retention of water and salt (invisible edema)

Practical Therapeutics

Realistic application of the principles of artificial hypercortinism to he treatment of the individual patient by the general practitioner is urrently limited as the result of questionable efficacy of commercially vailable products inadequate supply and excessive cost of potent aterial incomplete experiences in many conditions in which cortone ACTH conceivably may be of extraordinary value and insufficient ne for thorough assimilation of the mass of data currently being embled

For this reason the undernoted suggestions must be regarded as tative and subject to change with accumulation of new facts and ilability of new products

1 At the time of this writing (May 1950) the only adrenal cortical paration that possesses the full properties of compound E is cortone ck) This product may be obtained on application by the qualified ician to Dr J M Carlisle Medical Director Rahway New Y

Currently cortone is only allocated for conditions of great urgency marketed in 12 cc vials which contain a total of 300 mg (1 cc = r)

Keep cortone at room temperature It must not be refrigerated njections intramuscularly in an average initial dose of 100 mg every eight hours for 3 doses Follow by maintenance doses of every twelve hours for two doses and 50 mg every twelve hereafter until the maximum therapeutic response is obtained d that serious undesirable manifestations are not previously or eously encountered

hen the maximum response to cortone has occurred reduce e in stepwise fashion At 2 or 3 day intervals cut down the l dose by 10–15 mg until the total daily dose is 50 mg given divided doses at 12 hour intervals and then as a single daily mprovement persists give 100 mg every second day Should ant relapse occur re establish the daily dose of 100 mg aximum response again is evident Thereafter make another o diminish the individual dose in stepwise fashion as pre ndicated

the event that the expected therapeutic response is not within four to five days after initiation of cortone therapy daily dose to 200 mg Inject 4 cc every 12 hours for four en if possible return to 50 mg dose twice daily

rrently supplies of ACTH necessarily are held even more the Armour Laboratories To apply for ACTH communicate John R Mote Director of Medical Research of the Armour ies Chicago Illinois

EFFECTS OF ARTIFICIAL HYPERCORTINISM (*Continued*)

Anaphylatoxin

Production inhibited suggesting that patient with artificially induced hyper cortinism has greater resistance to anaphylactic shock and other hypersensitivity reactions including serum sickness May prove future aid to prophylaxis and active treatment of acute hi tamine type hypersensitivity reactions

Antibody Circulating

Titers significantly decreased resulting in increased vulnerability of patient to bacterial invasion Practical suggestions include need for massive doses of indicated antibiotic and/or temporary intermis ion of cortisone or ACTH until infection is controlled

Appetite

Increa es strikingly with loss of symptoms due to hypersensitivity phenomena

Arthropathies

Rapidly ameliorated if due to perversions of the mechanisms of bodily defense (rheumatoid arthritis rheumatic fever etc)

Blood Coagulability

Blood ludding significantly decreased Po sible future application of this ob ervation to prevention and treatment of intravascular clotting in thrombophiles (p 4571)

Blood Pressure

No significant consistent changes Cortone may offset hypertensive effects of desoxycorticosterone

Body Temperature

Tends to revert to normal when fever is due to conditions amenable to artificial hypercortinism (Rheumatic fever rheumatoid arthritis disseminated acute lupus erythemato us peri arteritis nodosa etc)

Callus (in Fractures)

Formation inhibited in experimentally produced lesions of cortone treated animals

Capillary Tufts

Depression delays granulation of artificially induced wounds in normals but may favor antirheumatic effects

Carbohydrate

Under normal conditions but slight impairment of carbohydrate tolerance With very large doses of cortone or ACTH marked hyperglycemia with glycosuria In the treatment of rheumatic patients with a sociated or coincidental diabetes mellitus there may be marked reduction of carbohydrate tolerance with increased in ulin resistance uggesting an adrenocortical hyperglycemia

Corticosteroids

Urinary concentrations initially increased during artificial hypercortinism After long continued administration levels fall suggesting exhaustion of the glandular mechanism and exposing the patient to le sened respon es to emergency demands incidental to acute infections or indicated surgery

Elastic Tissue

Friability results in reddish striae particularly over thighs Most often seen in young girls under therapy

EFFECTS OF ARTIFICIAL HYPERCORTINISM (*Continued*)

Menstruation

Irregularities and amenorrhea apt to occur in adolescents with rheumatic fever

Muscle Smooth

Tonus and spasmosis inhibited presumably favoring relief of symptoms in urticaria angioneurotic edema and bronchial asthma

Potassium and Bicarbonate

Potassium diuresis may result in hypopota emia (p 731) with alkalosis Dis continue hormone and if nece sary introduce pota sium intravenously

Protein Total

Peduced when there is a fall in globulin moiety Apply observation practically to treatment of nephrosis when there is a disturbance of albumin-globulin ratio

Psyche

Euphoria probably secondary to relief of manifestations due to hypersensitivity phenomena More marked with cortone than ACTH At least one patient with rheumatoid arthritis became psychotic during the cour e of ACTH therapy (Mote p 538) Against this at lea t one schizophrenic showed marked psy chiatric improvement after daily injections of 100 mg for 3 weeks (Mote p 551)

Sebum

Acne vulgaris presumably due to increased androgenic activity Unde irable under any circumstance

Serum Albumin
Boo

Not significantly affected under normal condition but slightly increased when abnormal
fi
acuid n

Callus (in Fractures) rd the normal of increased concentrations occasionally observ

Formation inhibited in Only slight changes when normal conditions prevai animals

Capillary Tufts water may re ult in clinical edema best

Depression delays granulation of arth weight With discontinuance of hormone may favor antirheumatic effects liberated as manifest by pontaneous r di appearance of edema and rapid

Carbohydrate ttle importance in those with normal

Under normal conditions but slight impai en backwa d failure in the patient With very large doses of cortone or ACT encountered particularly in rheu glycosuria In the treatment of rheumatic pa nism appears desirable ob erve cidental diabetes mellitus there may be mark y limitation of salt and water tolerance with increa ed insulin resistance s retics (p 4305) Should mani hyperglycemia all efforts discontinuance of

Corticosteroids

Urinary concentrations initially increased dur s ion of blood content Apply After long continued administration levels fall glandular mechani m and exposing the patie emergency demands incidental to acute infectio

ons are normal or above nor

Elastic Tissue i decrea ed excretion Later

Friability results in reddi h striae particularly tion of the production of 17 young girl under therapy

Weight

Nutntional gains with increased appetite and diminution of symptoms result ing from hypersensitivity phenomena Rapid and tran_ tory gains more likely the result of retention of water and s lt (invisible edema)

Practical Therapeutics

Realistic application of the principles of artificial hypercortinism to the treatment of the individual patient by the general practitioner is currently limited as the result of questionable efficacy of commercially available products inadequate supply and excessive cost of potent material incomplete experiences in many conditions in which cortone or ACTH conceivably may be of extraordinary value and insufficient time for thorough assimilation of the mass of data currently being assembled

For this reason the undernoted suggestions must be regarded as tentative and subject to change with accumulation of new facts and availability of new products

1 At the time of this writing (May 1950) the only adrenal cortical preparation that possesses the full properties of compound E is cortone (Merck) This product may be obtained on application by the qualified physician to Dr J M Carlisle Medical Director Rahway New Jersey

2 Currently cortone is only allocated for conditions of great urgency It is marketed in 12 cc vials which contain a total of 300 mg (1 cc = 25 mg)

3 Keep cortone at room temperature It must not be refrigerated Give injections intramuscularly in an average initial dose of 100 mg or 4 cc every eight hours for 3 doses Follow by maintenance doses of 100 mg every twelve hours for two doses and 50 mg every twelve hours thereafter until the maximum therapeutic response is obtained provided that serious undesirable manifestations are not previously or simultaneously encountered

4 When the maximum response to cortone has occurred reduce daily dose in stepwise fashion At 2 or 3-day intervals cut down the individual dose by 10–15 mg until the total daily do e is 50 mg given at first in divided doses at 12 hour intervals and then as a single daily dose If improvement persists give 100 mg every second day Should a significant relapse occur re establish the daily dose of 100 mg until a maximum response again is evident Thereafter make another attempt to diminish the individual do e in stepwise fashion as pre viously indicated

5 In the event that the expected therapeutic response is not obtained within four to five days after initiation of cortone therapy increase daily dose to 200 mg Inject 4 cc every 12 hours for four doses Then if possible return to 50 mg dose twice daily

6 Currently supplies of ACTH necessarily are held even more tightly by the Armour Laboratories To apply for ACTH communicate with Dr John R Mote Director of Medical Research of the Armour Laboratories Chicago Illinois

7 ACTH is presently marketed as a peptin digestive product dissolved in saline solution Make injections intragluteally in the average daily dose of 100 mg given in divided quantities at 6–8 hour intervals

8 With a few exceptions ACTH and cortone may be used interchangeably Recall that the two products are not physiologically equivalent milligram for milligram Of ACTH 100 mg apparently stimulates the production of possibly 200 mg or more of cortone In calculating dosage therefore twice as many milligrams of cortone must be administered to equal the physiologic effect of any given amount of ACTH

9 For substitution endocrinologic effects in hypopituitarism choose ACTH since the anterior pituitary adrenocortical relationship is not reversible and cortone is without significant efficacy in the treatment of deficiencies of the master gland

10 In Addisonian adrenal cortical deficiency ACTH is valueless if there is not sufficient adrenal cortical tissue to respond to stimulation by adrenocorticotropic hormone On the other hand if there is sufficient functioning adrenal cortical tissue ACTH has the theoretical advantage at least that it is a pan adrenocortical stimulus and does not merely evoke secretion of 17 hydroxy 11-dehydrocorticosterone Finally since it acts by stimulation of adrenal cortical tissue ACTH may exhaust the residual or damaged adrenal cortical tissue hazarding a crisis at the time of drug withdrawal To offset this possible effect it is suggested that cortone therapy be continued after cessation of ACTH

11 Because it is more rapidly absorbed and metabolized give ACTH two to four times daily Cortisone may be injected only once or twice daily

12 Since ACTH is a foreign protein allergic hypersensitivity reactions may be encountered By contrast cortone is a synthesized molecule to which hypersensitivity reactions apparently do not occur

13 Whereas cortone is a pure chemical ACTH may be contaminated by posterior pituitary substance and hence occasionally may give pharmacologic evidences of the impurity through production of mild abdominal cramps flatus and nausea

14 A rarer contaminant of ACTH is secretion from pars intermedia which has produced transitory pigmentation

15 The most striking measurable difference between cortone and ACTH is the production by the latter of eosinopenia

16 If the practitioner is unable to obtain ACTH or cortone he may try substitute preparations For example frequent subcutaneous or intramuscular injections of adrenalin hydrochloride (epinephrine) using 0 5 to 1 cc of 1 1000 solution may evoke adrenal cortical secretion Provided that uncomfortable sympathomimetic manifestations are not produced (p 3869) this readily available and relatively inexpensive substitute may be tried in the therapy of definitively responsive syndromes such as rheumatoid arthritis If a result is not obtained within a very short time injections are best abandoned

17 Of available steroids the practitioner may give intramuscular injections of doca (Roche) or percorten (Ciba) peanut oil solutions of

desoxycorticosterone acetate or of prenolon (Schering) which is Δ 5 pregnenolone The first two are of similar strength and the average dose is 1 cc equivalent to 5 mg The dose of prenolon is 100 to 200 mg Following the lead of European investigators intravenous injections of 100 mg of ascorbic acid (vitamin C) are given within five minutes of intramuscular injection of steroid In this way it is assumed that con version of desoxycorticosterone to cortisone is encouraged within the human economy Both favorable and disappointing results have been reported A trial period of a week or ten days is justified With an encouraging response therapy may be continued if definitive results are not obtained in the trial period injections are better abandoned

18 Irrespective of the product employed bear in mind that none of these preparations is curative or even specific Like opiates in the relief of pain and antihistamines in the relief of acute histamine type hyper sensitivity reactions adrenal cortical and adrenocorticotropic products merely afford symptomatic relief If the etiologic mechanism is still operative when they are withdrawn symptoms will recur Only in the event that the operative cause is transitory (as in histamine type hypersensitivities) will there be relatively lasting alleviation of distress

19 Irrespective of the condition under therapy and irrespective of the auspices under which injections are given responses to cortone and ACTH include both desirable and undesirable manifestations The latter are not toxicologic side reactions they are as physiologic as desirable effects The therapist must take stock daily and decide whether the game is worth the candle If desirable effects are strik ing and undesirable merely annoying therapy may be continued Contrariwise even in the face of a satisfactory therapeutic result if objective manifestations are disturbing to the patient (hirsuties acne) or to the therapist (weight gain due to retention of salt and water glycosuria hyperglycemia) administration of hormone must be reduced or if necessary abandoned

20 In summary Favorable results have been reported by Hench and Mote in some cases of rheumatic fever pneumonia tuberculosis virus pneumonitis atopic dermatitis bronchial asthma disseminated neurodermatitis non specific ulcerative colitis the leukemias peri arteritis nodosa hepatitis and alcoholism ACTH has also been tried with good results in various ophthalmologic conditions (J A M A 142 1271 1950)

21 In analogy to these encouraging results a trial of cortone or ACTH would seem justified in all types of severe or persistent his tamine type or tuberculin type hypersensitivity reactions infections in which the invasive element is associated with significant or crippling bacterial hypersensitivity such as meningococcus infections rabies or mycoses neoplastic diseases in which the malignant cell is a hema tologic component and chronic or potentially fatal diseases for which no other form of therapy is presently available

Results in the treatment of poliomyelitis and carcinoma have been discouraging

ADRENERGENS

The pharmacology and therapeutics of the adrenergen have received previous consideration (p 3876) Introduction of new preparations requires re assessment of products previously described in comparison with those recently made available

ADRENERGENS

Chemical Name	Available Products
2 Aminoheptane racemic	*Tuamine* (Lilly) Inhaler and nasal drops
Amphetamine	*Benzedrine benzedrine sulfate* (S K F) Inhalers and tablet
Ephedrine U S P	Alkaloid derived from ma huang Marketed as hydrochloride and sulfate Effective orally (p 3880)
Ephedrine racemic	*Racephedrine hydrochloride* or *sulfate* (Upjohn) Marketed in capsules and solution Nasal drop
Epinephrine	*Adrenalin* (Parke Davis) *suprarenalin* (Armour) and *suprarenin* (Winthrop)
Isopropylarterenol	Bronchodilators marketed as *isuprel* (Winthrop) *isonorin* (Smith) *orthodoxine* (Upjohn) in U S A and as *aludrine* in Europe See also text
Methamphetamine	*Desoxyn* (Abbott) and *norodin* (Endo) Use as amphetamine (p 3882)
Naphazoline	*Privine* (Ciba) Nasal drops
Phenylephrine	*Neosynephrine* (Winthrop) p 3882
Phenylpropanolamine	*Propadrine* (Sharp & Dohme) p 3883
Phenylpropylmethylamine	*Vonedrine* (Merrell) Resembles amphetamine (p 3882)

PHARMACOLOGY AND THERAPEUTICS OF ADRENERGENS

Indication	Comment
Addison s disease	Of no value
Alcoholism	Try oral benzedrine desoxyn or norodin (5 to 20 mg)
Allergy	Prefer antihistamines If unsuccessful combine oral adrenergen (ephedrine benzedrine desoxyn) with antihistamine for cumulative anti allergic effect Cerebral depression from antihistamine is offset by cerebral stimulation of adrenergen
Anaphylaxis	Epinephrine 1 10 000 or 1 1000 intramuscularly or intravenously with antihistamine
Asthma	See Bronchoconstriction
Bleeding	*For oozing apply 1 1000 epinephrine*
Bronchoconstriction	In asthma Epinephrine (1 100) isuprel or isonorin (1 200) spray for nose or throat Isuprel or isonorin (10 to 15 mg) sublingually Ephedrine (25 to 50 mg) or orthoxine (100 mg) orally Epinephrine (1 1000 aqueous or 1 500 in oil) parenterally The patient receiving adrenergen for the first time must be closely observed Sufficient drug is given to control symptoms provided that side reactions particularly tachycardia cerebral stimulation and tremor do not occur before the therapeutic effect of the preparation has been accomplished
Circulatory depression	Especially in acute barbiturate poisoning consider oral adrenergen if mild parenteral amphetamine or desoxyn if severe
Circulatory stimulation	Avoid except in forward failure (shock)

Forward failure	Ephedrine 25 or 50 mg epinephrine 1 1000 or neosyne phrine 1% parenterally
Hyperinsulinism	For hyperglycemic effect in spontaneous or therapeutic hypoglycemia inject parenterally 1 1000 epinephrine
Hypotension	In chronic hypotension oral ephedrine (25 to 50 mg) or benzedrine (2 5 to 10 mg)
	In acute hypotension inject epinephrine 1 1000 cautiously
Mydriasis	4% ephedrine 0 5% neosynephrine or 1% paredrine
	No elevation of intra-ocular tension
Narcolepsy	Use benzedrine desoxyn or norodin (2 5 to 10 mg)
Nasal congestion	Inhalers benzedrine vonedrine tuamine
	Nasal jellies ephedrine (1%) privine (0 05%) neosyne phrine (0 5%) propadrine (0 66%)
	Nasal solutions ephedrine (3%) epinephrine (1 1000) privine (0 1 or 0 05%) neosynephrine (1/8, 1/4 or 1%) propadrine (1 or 3%) racephedrine (1%) tuamine (1 or 2%)
	Oral use of antihistamines appears far preferable to nasal instillation of adrenergens Antihistamines may be combined with small doses of adrenergens such as ephedrine benzedrine or desoxyn
Obesity	Oral benzedrine desoxyn or norodin 2.5 to 10 mg before meals on arising and at luncheon. If given later may produce cerebral stimulation sufficient to result in insomnia
Paralysis agitans	Prefer other muscle relaxants (artane parpanit) with fewer side effects but try benzedrine or desoxyn (2 5 to 10 mg)
Serum sickness	See Allergy above
Shock	See Forward Failure above
Stokes Adams disease	Oral ephedrine (25 to 50 mg) as prophylactic
Vasodilatation	For local effect, combine epinephrine 1 1000 with anesthetic for systemic effect see Forward Failure above

ADRENOCORTICAL DEFICIENCY

[Addison s Disease]

Studies of the adrenal cortex and of the syndrome of adrenal insufficiency as described by Addison (p 1271) continue to preoccupy many clinics despite the rarity with which the disturbance is encountered in clinical practice Thus in thirty one years of an active private practice we have encountered only one case

Pending large scale production of a potent adrenal cortical extract containing all hormonal components and or its anterior pituitary adrenocorticotropic factor the treatment of Addison s syndrome will probably continue to be laborious and not wholly satisfactory Hence the practitioner might consider reference of his patient to special investigators actively engaged in the study of adrenocortical problems

Treatment of the Crisis in Addison s Disease

Treatment of the Addisonian crisis continues to be complicated and hazardous The technic employed by Sorkin and Soffer differs somewhat from that previously described (p 1278)

1 Set up an intravenous drip of physiologic saline with 5% glucose Do not exceed 2500 cc per twenty four hours discontinue as soon as fluids are tolerated orally

2 Into the tubing of the intravenous drip inject directly 20 cc of aqueous cortical extract (p 4144) Place another 20 cc in the drip for maintenance

3 Inject intramuscularly 5 to 10 mg of desoxycorticosterone acetate in oil Repeat in twelve hours if necessary and then reduce the dose to 5 mg daily if all is well After the crisis has subsided reduce the dose gradually to 1 to 2 mg daily unless the patient evinces an excessive increase in blood pressure retention of water or evidences of rapid increase in the size of the heart

4 Two to four hours after injection of desoxycorticosterone acetate deposit 5 cc of lipocortical extract intramuscularly repeat every two or four hours if necessary

5 If there are evidences of infection or the patient is febrile introduce 600 000 units of procaine penicillin G in oil with 2% aluminum monostearate

6 Maintain body warmth with blankets

7 Administer oxygen if necessary

8 Transfuse 500 cc of citrated blood if necessary

9 Avoid morphine its derivatives and substitutes

Maintenance Therapy in Addison s Disease

1 Inject a sufficient amount of desoxycorticosterone acetate daily to maintain weight blood pressure and well being The average dose approximates 0 5–1 5 mg

2 While the dose of desoxycorticosterone acetate is being determined give a fixed daily supplement of 4 gm of sodium chloride After the dose of extract has been determined decrease amount of sodium chloride if edema or hypertension occurs increase the dose during hot weather during the presence of infection or if signs of Addison s syndrome develop

3 Consider replacement of injection therapy by implantation of pellet Implant approximately 1 pellet of 125 mg for each 0 5 mg required for daily maintenance in injection therapy

ADRENOCORTICAL EXTRACTS

See Corti one and Compound E (p 4145)

ADRENOCORTICOTROPIC HORMONE ANTERIOR PITUITARY (ACTH)

See p 4146

AEROBACTER AEROGENES INFECTIONS

Principles of Diagnosis and Treatment

1 A aerogenes (B aerogenes) produces no characteristic clinical syndrome The diagnosis of invasion rests on bacteriologic identification of the organism

2 A aerogenes a gram negative bacillus is sensitive to aureomycin chloramphenicol the streptomycins and sulfonamides

3 Of low virulence A aerogenes usually is not a primary invader unless (a) the general resistance of the host is lowered (b) there is impairment of local organ integrity or (c) prior invasion by an organism of greater pathogenicity has occurred

4 Whether A aerogenes produces systemic bacteremia or local inflammation (urinary biliary pulmonary meningeal) anti infective therapy must be supplemented by measures to (a) increase the general resistance of host (b) remove impediments threatening the functional capacity of the infected organ (renal or biliary calculi etc) and (c) eliminate accompanying primary invaders

Practical Management

Immediate Care

1 Obtain urine and hemogram get blood for grouping and cross matching

2 Check physical status for evidences of chronic or debilitating disease e glycosuria or renal insufficiency

3 Depending on estimated severity of infection give orally a priming dose of 30 to 60 mg per kilo (2 to 4 gm for adult weighing 150 lbs) of chloramphenicol or aureomycin Give 2 capsules in milk soup or cream cheese every few minutes until total dose is administered (8 to 16 products each of 250 mg)

4 Get plain radiographs of potentially involved organs (chest and biliary or genito-urinary tracts)

Continuing Care (Favorable Course)

1 Maintain antibiotic levels with 0 5 gm chloramphenicol or aureomycin (2 products of 250 mg each) every four to six hours

2 Transfuse 500 cc of citrated blood if red cells are less than 3 000 000 or hemoglobin below 7 5 gm

3 Order high calory diet (p 671)

4 Arrange for contrast roentgenograms of biliary and urinary tracts (cholecystogram and intravenous pyelogram)

5 Consult with surgeon if biliary tract is involved Discuss interval operative intervention (cholecystectomy etc)

6 Request urologist to perform cystoscopy and retrograde pyelography (p 2251) Consider interval operative procedure if organic disease is demonstrable

1 Set up an intravenous drip of physiologic saline with 5% glucose Do not exceed 2500 cc per twenty four hours discontinue as soon as fluids are tolerated orally

2 Into the tubing of the intravenous drip inject directly 20 cc of aqueous cortical extract (p 4144) Place another 20 cc in the drip for maintenance

3 Inject intramuscularly 5 to 10 mg of desoxycorticosterone acetate in oil Repeat in twelve hours if necessary and then reduce the dose to 5 mg daily if all is well After the crisis has subsided reduce the dose gradually to 1 to 2 mg daily unless the patient evinces an excessive increase in blood pressure retention of water or evidences of rapid increase in the size of the heart

4 Two to four hours after injection of desoxycorticosterone acetate deposit 5 cc of lipocortical extract intramuscularly repeat every two or four hours if necessary

5 If there are evidences of infection or the patient is febrile introduce 600 000 units of procaine penicillin G in oil with 2% aluminum monostearate

6 Maintain body warmth with blankets

7 Administer oxygen if necessary

8 Transfuse 500 cc of citrated blood if necessary

9 Avoid morphine its derivatives and substitutes

Maintenance Therapy in Addison s Disease

1 Inject a sufficient amount of desoxycorticosterone acetate daily to maintain weight blood pressure and well being The average dose approximates 0 5–1 5 mg

2 While the dose of desoxycorticosterone acetate is being determined give a fixed daily supplement of 4 gm of sodium chloride After the dose of extract has been determined decrease amount of sodium chloride if edema or hypertension occurs increase the dose during hot weather during the presence of infection or if signs of Addison s syndrome develop

3 Consider replacement of injection therapy by implantation of pellet Implant approximately 1 pellet of 125 mg for each 0 5 mg required for daily maintenance in injection therapy

ADRENOCORTICAL EXTRACTS

See Cortirone and Compound E (p 4145)

ADRENOCORTICOTROPIC HORMONE ANTERIOR PITUITARY (ACTH)

See p 4146

Available Products

Aerosporin is not yet commercially available

Pharmacology

Against gram negative bacteria aerosporin has a potency that is 10 to several 100 times that of streptomycin Experimentally it appears especially protective against *H* pertussis *E* typhosa and *H* bronchi septicus It apparently has no influence on M tuberculosis

Aerosporin is not absorbed from the intestine and hence cannot be given orally Injected intramuscularly it disappears quickly from the blood so that doses must be repeated at 4 hour intervals

Therapeutics

Intramuscular injections of 0 4 to 0 8 mg at 4 hour intervals for five days appear effective in the control of pertussis in children In view of the efficacy in pertussis of orally available non toxic aureomycin and chloramphenicol it is unlikely that manufacture of aerosporin will receive encouragement and support

Toxicology

Aerosporin is not hemolytic and is no more leukotoxic than penicillin Its minimum lethal intravenous dose is at least 75 times the average therapeutic dose so that it has a wide margin of safety Unfortunately it is nephrotoxic at times perhaps due to impurity If this factor can be eliminated aerosporin may be later added to the growing list of useful and non toxic antibiotics

ALKALIGENES FECALIS INFECTION

B alkaligenes fecalis is a gram negative organism which resembles Aerobacter aerogenes clinically bacteriologically and in its antibiotic sensitivities The Principles of Treatment and the Practical Management relevant to infections caused by Aerobacter aerogenes are equally applicable to those due to Alkaligenes fecalis

ALLERGY

(Hypersensitivity)

In the introduction to the subject of Allergy (p 547) attention was directed to the paradox that penicillin a powerful anti infective agent is a derivative of a potentially invasive micro organism whereas perversions of mechanisms of host defense may produce serious and even fatal clinical reactions

Originally attention centered mostly on acute histamine type allergic

Continuing Care (Unfavorable Course)

1 With gastric intolerance either to chloramphenicol or aureomycin substitute other product in similar dose

2 With continued gastric intolerance to both substitute streptomycin by intramuscular injection Give priming dose of 1 gm followed by maintenance doses of 0 5 gm thrice daily

3 With continued evidences of infection supplement chloramphenicol aureomycin or streptomycin with (a) penicillin to eliminate potentially resistant primary invaders or (b) sulfonamide for synergistic antibiotic activity against A aerogenes

4 If penicillin is used give priming dose intramuscularly of an aqueous suspension of 200 000 units of crystalline penicillin G with 600 000 units of crystalline procaine penicillin G Continue with 100 000 units penicillin G and 300 000 units procaine penicillin G once or twice daily

5 If sulfonamide is used give priming oral dose of 1 5 to 2 0 gm each of sulfadiazine and sulfamerazine with 4 gm sodium bicarbonate If stomach is intolerant due to causes other than sulfonamide toxicity inject loading dose intravenously using 2 5 gm each of sodium sulfadiazine and sodium sulfamerazine in 200 to 500 cc of sterile diluent preferably molar lactate (p 4546) Maintain sulfonamide levels with 0 5 to 1 gm of each thrice daily

6 Start antihistamine prophylactically Give 200 mg daily of pyribenzamine or benadryl

Continuing Care (Progressively Unfavorable Course)

1 In consultation with surgeon and urologist renew search for feeding focus

2 In absence of toxicity blanket bacterial spectrum with aureomycin or chloramphenicol streptomycin penicillin and sulfonamide

3 Increase penicillin levels by substituting crystalline procaine penicillin G in oil with 2% aluminum monostearate Continue 600 000 units daily at first Double unitage later if necessary

3 Increase dose of aureomycin or chloramphenicol With meningeal involvement remove 10 cc of cerebrospinal fluid and instill 8 cc of streptomycin (1 cc = 50 mg)

4 Increase dose of sulfonamide unless toxicity is observed in daily urinalyses and hemograms

5 Repeat transfusion if needed

AEROSPORIN

An antibiotic produced by B aerosporus an aerobic spore bearing bacillus probably identical with B polymyxa from which polymyxin is derived (p 4480)

Hypersensitivity and Active Immunity Clinically phenomena of hypersensitivity appear diametrically opposed to processes of active immunization Immunologically however mechanisms of resistance and hypersensitivity possess many common characteristics

Resistance To the best of pre ent knowledge specific defensive antibody is chemically a globulin manufactured by connective tissue cells fibroblasts lymphocytes monocytes vascular endothelium etc Under normal conditions after inoculation with antigen the patient develops decreasing responses or resistance to subsequent exposures (active immunity)

It has been suggested that in active immunity parent cells manu facture defensive substance and then shed protective globulin more or le s completely Later when antigen and antibody meet their merger primarily occurs extracellularly Under these circumstances antibody tends to protect the host against antigen and the process of active immunization has begun

Hypersensitivity In those perversions of mechanisms of bodily defense known as hypersensitivity reactions introduction of antigen is also followed by production of antibody Unfortunately however anti body is held partially or relatively completely by parent cells When antigen is reintroduced later merger between antigen and antibody occurs intracellularly in whole or in part with disastrous effects to cell and host In place of increased resistance to infection clinical manifestations are found which are presently grouped as allergic hyper sensitivities Upon subsequent exposure to specific antigen the tissues respond with increasing intensity

Resistance *or* Hypersensitivity What determines whether a given individual shall respond by resistance by hypersensitivity or by both mechanisms remains as yet unknown Various theories have been advanced (1) The character of antibody differs in the two conditions (2) antibodies are alike and the variable is the character of response by parent cells and finally (3) the determining factor is adreno cortical hormone which in turn is regulated by an anterior pituitary adrenocorticotropic hormone

Currently it seems most likely that the second and third hypotheses may be fitted to explain the strange phenomena Quite likely it is antibody that is constant and cellular response that varies depending on the influences of hormonal factors Thus in the therapeutic state of healthful active immunity obliging parent cells liberate antibody under the influence of adrenocortical hormone meeting of antigen and antibody occurs in circulating fluid and the host is abetted in his defense against alien intruding substance By contrast in the baneful condition of hypersensitivity antibody is retained in parent cells with greater or lesser tenacity meeting of antigen and antibody occurs within the cell and resulting reactions are detrimental if not lethal to cell and host

In acute histamine type allergic hypersensitivity intracellular union of antigen and antibody liberates histamine or histamine like substances In chronic tuberculin type allergic hypersensitivities noxious products

hypersensitivities for in these clinical reactions the causal relationship between exposure to offending allergen and strange tissue responses was readily established Currently renewed interest in chronic tuberculin type allergic hypersensitivity reactions has been stimulated by researches in many clinics and laboratories

Terminology In the study and treatment of patients suffering from allergies many difficulties stem from insufficient knowledge of mechanisms which produce this strange disorder others arise from the bewildering terminology of the subject The reader is under the semantogenic handicap of attempting to define each author s individual use of the terms allergy anaphylaxis atopy Koch s phenomenon Arthus phenomenon Prausnitz Kustner reaction Schwartzman phenomenon histamine type hypersensitivity tuberculin type hypersensitivity etc

At hazard of offense to the more enlightened the label of *allergic hypersensitivity* is used in the current text to cover all perversions of mechanisms of host defense Other generally accepted technical terms are included when their use clarifies but does not confuse the presentation

Etiology Many substances are capable of inducing allergic hyper sensitivity Originally it was believed that sensitizing agents were exclusively microbic (bacterial hypersensitivity) Later the concept was broadened to include any protein molecule (protein hypersensitivity) Currently the roster includes new molecules formed by union of non protein with body protein as in the case of salicylates iodides sulfonamides etc

The present list of proven offending allergens includes heterologous serums pollens contactual substances encountered in cosmetics or industry food substances physical agents psychic trauma inorganic and organic derivatives of micro organisms helminths plants and animals products of industrial chemistry and drugs and medicinals given with therapeutic intent including commonly prescribed medicaments such as salicylates iodides sulfonamides phenolphthalein dilantin antithyroid preparations and endocrine products (insulin heparin liver extract etc)

Consistent with fact the physician must be prepared to accept the following heresies (1) alterations in mechanisms of body defense may convert many relatively harmless substances into highly toxic agents (2) drugs serums and potent antibiotics may produce in the hyper sensitive untoward manifestations that vary from discomfort and annoyance to incapacitation or even fatal illness

Bacteriology and Serology Negative evidence favoring the theory of a hypersensitivity reaction is afforded by bacteriologic and serologic studies in suspected clinical disturbances which *may have many fea* tures of infection i e fever leukocytosis increased erythrocyte sedimentation rate local inflammation etc Yet in none have living organisms been recovered from tissues or blood despite extensive bacteriologic studies Serologic findings are equally unrevealing except for demonstration of antistreptolysin and antifibrinolysin in rheumatic fever

ACUTE HISTAMINE TYPE ALLERGIC HYPERSENSITIVITIES

Clinical Syndrome	Usual Offending Allergen	Usual Shock Organ
GENERAL		
Anaphylactic shock (p 549)	Serum (For treatment see p 4187)	Smooth muscle of vessels and bronchi blood.
Serum sickness (p 549)	Serum. (For treatment, see p 4519)	Skin, bronchial muscle mucous membranes
RESPIRATORY		
Seasonal vasomotor rhinitis (Hay fever p 2097)	Pollen. (For treatment, see p 4478)	Nasal mucous membrane
Non seasonal vasomotor rhinitis (p. 2098)	Bacteria (For treatment, see p 4249)	Nasal mucous membrane
Bronchial asthma (p 2101)	Pollen, bacteria digestants psychogenic (For treatment see p 4270.)	Bronchial musculature
Eosinophilic pneumonitis (Loeffler's syndrome p 2104)	Bacteria (For treatment, see p 4318)	Pulmonary alveoli
TEGUMENTARY		
Atopic dermatitis (Eczema p 3342)	Digestants. (For treatment, see p 4329)	Skin.
Contact dermatitis (dermatitis venenata p 3330)	Poison ivy drug cosmetics chemicals (For treatment, see p 4297)	Skin.
Dermatitis medicamentosa (p 3335)	Drugs chemicals cosmetics (For treatment, see p 4306)	Skin, mucous membranes.
Urticaria (hives p 3345)	Serum digestants drugs bacteria, physical energy psychogenic	Skin and mucous membranes
Angioneurotic edema (p 3349)	As urticaria	As urticaria
Disseminated neurodermatitis (p 3343)	Digestants psychogenic	Skin.
Idiopathic pruritus (p 1916)	Psychogenic digestants bacteria helminths	Skin.
OCULAR		
Vernal conjunctivitis (p 1651)	Pollens chemical	Conjunctiva
Phlyctenular keratoconjunctivitis (p 1650)	Pollens bacteria	Conjunctiva and cornea
Sympathetic ophthalmia (p 1565)	Lens prot in	Uninjured eye
Uveitis (p 1632)	Bacteria	Choroid and retina.
MISCELLANEOUS		
Allergic arthropathy (p 2810 2878)	Serum bacteria drugs	Synovia and periarticular structures
Physical allergy (p 552)	Heat cold light solar energy (For treatment, see p 4465)	Skin, kidney
Psychogenic allergy (p 552)	Psychic trauma	Skin, bronchial musculature
Endocrine allergy	To insulin liver extract heparin etc	Local reaction at injection site fever eosinophilia.
Insect allergy (p 936 3197)	Bees wasps hornets scorpions	Skin mucous membranes

of intracellular merger have not yet been identified Nevertheless in either instance failure of parent cells to liberate antibody appears due to lack of adrenocortical hormone which in turn may result from deficient stimulus from anterior pituitary adrenocorticotropic factor

That the hypothesis is of more than academic significance is illustrated by palliative responses to histamine antagonists in acute histamine type allergic hypersensitivities and by symptomatic relief in chronic tuberculin type allergic hypersensitivity reactions when adrenocortical hormone pituitary adrenocorticotropic factor (ACTH) or steroids *having adrenocortical activity such as cortisone (compound E)* are administered

Resistance *and* Hypersensitivity According to expert opinion the reactions of active immunity and of hypersensitivity are not mutually exclusive In the words of Rich (Harvey Lectures 1946/47) Acquired resistance is not dependent upon hypersensitive inflammation for its effective operation when the capacity to react with hypersensitivity *inflammation is eliminated the immunity mechanism operates unim*paired and the tissues are spared from the damaging effects of hypersensitivity

ACUTE HISTAMINE TYPE ALLERGIC HYPERSENSITIVITY REACTIONS

Whether hereditary (atopic) or acquired (anaphylactic) acute histamine type allergic hypersensitivity appears due at least in part to production or liberation of histamine or histamine like substances

The clinical manifestations of histamine type hypersensitivity are many and varied and bear confusing labels (see Table p 4167) Some are named for offending allergens (serum sickness dermatitis medicamentosa) others for shock organs (vasomotor rhinitis vernal conjunctivitis) and still others for pathologic response (angioneurotic edema eosinophilic pneumonitis) Whatever the terminology each syndrome is clearly an individual response to a profound disturbance of mechanisms of defense Hence the astute practitioner devotes himself primarily to a search for the sensitizing factor or factors and regards other considerations as accessory

Common Denominators Histamine type clinical disturbances exhibit these common features Each is due to perversion of normal responses of the body to introduction of foreign substance in each the structure most affected is usually but not always the portal of entry for allergen in each the response is disseminated beyond the portal of entry suggesting that the offending reaction is produced or accompanied by liberation of some hematogenously transported substance provocative antigen in each is innocuous for those who do not exhibit hypersensitivity there is relatively rapid development of clinical manifestations after exposure to specific noxious substance inflammatory reactions are characterized by increased vascular permeability exudation spasm of smooth muscle and eosinophilia The clinical syndromes may be duplicated by re exposures to offending antigens imitation of clinical syndromes in part follows injection of histamine in the laboratory circulating antibody is demonstrable passive transfer to the experi

ACUTE HISTAMINE TYPE ALLERGIC HYPERSENSITIVITIES

Clinical Syndrome	Usual Offending Allergen	Usual Shock Organ
GENERAL		
Anaphylactic shock (p 549)	Serum (For treatment see p 4187)	Smooth muscle of ves sels and bronchi blood.
Serum sickness (p 548)	Serum (For treatment see p 4519)	Skin, bronchial mus cle mucous mem branes
RESPIRATORY		
Seasonal va omotor rhinitis (Hay fever p 2097)	Pollen (For treatment see p 4478)	Nasal mucous mem brane
Non essonal vasomotor rhinitis (p 2098)	Bacteria (For treatment, see p 4249)	Nasal mucous mem brane
Bronchial asthma (p 2101)	Pollen, bacteria digest ant, psychogenic (For treatment see p 4270)	Bronchial musculature
Eosinophilic pneumonitis (Loeff ler s syndrome p 2104)	Bacteria (For treatment see p 4318)	Pulmonary alveoli
TEGUMENTARY		
Atopic dermatitis (Eczema p 3342)	Digestants (For treatment see p 4329)	Skin
Contact dermatitis (dermatitis venenata p 3330)	Poi on ivy drugs cos metics chemicals (For treatment see p 4297)	Skin.
Dermatitis medicamentosa (p 3335)	Drugs chemicals cos metics (For treatment see p 4306)	Skin mucous mem branes
Urticaria (hives p 3345)	Serum digestants drugs bacteria phy ical en ergy psychogenic	Skin and mucous m m branes
Angioneurotic edema (p 3349)	As urticaria	As urticaria
Disseminated neurodermatitis (p 3343)	Digestants psychogenic	Skin
Idiopathic pruritus (p 1916)	Psychogenic digestants bacteria helminths	Skin
OCULAR		
Vernal conjunctivitis (p 1651)	Pollens chemicals	Conjunctiva
Phlyctenular keratoconjunctivitis (p 1650)	Pollens bacteria	Conjunctiva and cor nea
Sympathetic ophthalmia (p 1565)	Lens protein	Uninjured eye
Uveitis (p 1632)	Bacteria	Choroid and retina
MISCELLANEOUS		
Allergic arthropathy (p 2810 2878)	Serum bacteria drugs	Synovia and periarti cular structures
Physical allergy (p 552)	Heat cold light solar en ergy (For treatment see p 4465)	Skin kidneys
Psychogenic allergy (p 552)	Psychic trauma	Skin bronchial mus culature
Endocrine allergy	To insulin live extract heparin etc	Local reaction at in jection site fever eosinophilia
Insect allergy (p 936 3197)	Bees wasps hornets scor pions	Skin mucous mem branes

ACUTE HISTAMINE TYPE ALLERGIC HYPERSENSITIVITIES (*continued*)

Clinical Syndrome	Usual Offending Allergen	Usual Shock Organ
MISCELLANEOUS		
Meniere s di ease (p 1486)	Unknown	Internal ear (?)
Migraine (p 1506)	Dige tant, psychogenic	Cerebral blood ves sels (?)
Epilepsy (p 1515)	Dige tants psychogenic unknown	Central nervous sys tem
Motion ickness (p 1487 3876)	Unknown (For treatment, see p 4218)	Unknown
Gastro intestinal allergy (p 1767)	Food tuffs (For treatment see p 4329)	Gastro inte tinal mu co a and musculature
Urinary allergy	Unknown streptococcus	Mucosa of bladder and urethra kid eys (acute nephritis p 2373)
Gynecologic allergy	Psychogenic unknown	Uterine musculature (dysmenorrhea)

mental animal may be accomplished symptomatic relief is obtained to greater or lesser degree by use of adrenergens and antihistamines cures may follow elimination of offending antigen or desensitization (p 4191)

Exceptions Many claims in the previous paragraph require qualifica tion Thus in dermatitis medicamento a due to ingested drug the portal of entry for offending antigen is not most affected and the shock organ u ually is the kin in pollen hypersensitivities the character of the re sponse may be independent of antigen and dependent on patient response for one sensitized individual may develop hay fever while another suffers a bronchial asthma That there is more to histamine type hypersensitivity than mere liberation of histamine is attested by failure of injected histamine to reproduce all clinical manifestations and by failure of adrenergens and antihistamines completely to palliate much less cure presenting clinical disturbances

CHRONIC TUBERCULIN TYPE ALLERGIC HYPERSENSITIVITIES

The chronic tuberculin type allergic hypersen itivities otherwise variegated and puzzling have the undernoted characteristics in com mon suggesting their unitarian origin

1 Etiology and pathogene is otherwise unknown
2 Clinical manifestations usually suggest the operation of an infec tious element
3 Failure to respond to antibiotic agents
4 Manifestations not palliated by antihistamines or adrenergens
5 Negative bacteriologic and serologic findings
6 In many a precedent history of upper respiratory infection
7 In many a history of antecedent sensitivity reactions to food drugs pollens etc

8 Usual clinical course is characterized by remission and exacerba tion neither explicable on infectious basis
9 Pathologically they exhibit some if not all of the polymorphous manifestations produced in sensitized experimental animals exposed to bacterial and non bacterial antigens such as hetero logous serums salicylates sulfonamides etc
10 Preliminary investigations strongly intimate that each syndrome may respond to steroids possessing the activity of certain adrenal cortical hormones (cortisone)

CHRONIC TUBERCULIN TYPE ALLERGIC HYPERSENSITIVITIES

Clinical Syndrome	Usual Offending Allergen
BLOOD AND VASCULAR SYSTEMS	
Rheumatic fever (pp 186 and 4493)	Hemolytic streptococcus
Peri-arteritis nodosa (p 1027 and 4460)	Serum drugs (sulfonamide iodide dilantin salicylate thiourea and phenolphthalein)
Thrombo-angiitis obliterans (p 1049)	Tobacco (?)
Atypical verrucous endocarditis (Libman Sachs) (p 1019)	Hemolytic streptococcus (?)
Non bacterial thrombotic endocarditis (p 1027)	?
Visceral angiitis (p 1027)	?
Purpuras (p 3243)	Hemolytic streptococcus drugs
Erythema multiforme (p 3161 and 4323)	Hemolytic streptococcus drugs etc
Paroxysmal hemoglobinuria (p 1075)	Cold plus syphilis
NERVOUS SYSTEM	
Encepha opathies	Rabi s vaccine and various viruses includ ing tho e of chickenpox measles small pox etc (pp 440 and 445)
Peripheral neuropathies (p 1489)	As Encephalopathies
Multiple sclerosis (p 1504)	?
RESPIRATORY SYSTEM	
Eosinophilic pneumonitis (p 4318)	Hemolytic streptococci and other unidenti fied allergens
Chronic pneumonitis (pneumonopathy)	Abacterial pulmonary manife tations in rheumatic fever tuberculosis and particularly fungus invasions such as actinomycosis blastomycosis coccidioido mycosis etc
Pleuritis (pleuropathy)	As Chronic pneumonopathy
GENITO URINARY SYSTEM	
Chronic glomerulonephritis (p 2379)	Hemolytic streptococci etc
SKELETAL AND LOCOMOTOR SYSTEMS	
Rheumatoid arthritis (p 2910 and 4502)	Hemolytic streptococci (?) etc
Eosinophilic granuloma of bone (p 2843)	?
Gout (p 2867)	?
TEGUMENTARY SYSTEM	
Idiopathic pruritus (p 3178)	?
Purpura (p 3423)	Hemolytic streptococci drugs etc
Erythemas (pp 3374 3377)	Hemolytic streptococci drug etc
Scleroderma (p 3427)	?
Sarcoidosis (p 3271)	Tubercle bacilli (?)

ACUTE HISTAMINE TYPE ALLERGIC HYPERSENSITIVITIES (*continued*)

Clinical Syndrome	Usual Offending Allergen	Usual Shock Organ
MISCELLANEOUS		
Meniere s disease (p 1486)	Unknown	Internal ear (?)
Migraine (p 1506)	Digestants psychogenic	Cerebral blood vessels (?)
Epilepsy (p 1515)	Digestants psychogenic unknown	Central nervous system
Motion sickness (p 1487 3876)	Unknown (For treatment see p *4218*)	Unknown
Gastro intestinal allergy (p 1767)	Food tuffs (For treatment see p 4329)	Gastro intestinal mucosa and musculature
Urinary allergy	Unknown streptococcus	Mucosa of bladder and urethra kidneys (acute nephritis p 2373)
Gynecologic allergy	Psychogenic unknown	Uterine musculature (dysmenorrhea)

mental animal may be accomplished symptomatic relief is obtained to greater or lesser degree by use of adrenergens and antihistamines cures may follow elimination of offending antigen or desensitization (p 4191)

Exceptions Many claims in the previous paragraph require qualification Thus in dermatitis medicamentosa due to ingested drug the portal of entry for offending antigen is not most affected and the shock organ usually is the skin in pollen hypersensitivities the character of the response may be independent of antigen and dependent on patient response for one sensitized individual may develop hay fever while another suffers a bronchial asthma That there is more to histamine type hypersensitivity than mere liberation of histamine is attested by failure of injected histamine to reproduce all clinical manifestations and by failure of adrenergens and antihistamines completely to palliate much less cure presenting clinical disturbances

CHRONIC TUBERCULIN TYPE ALLERGIC HYPERSENSITIVITIES

The chronic tuberculin type allergic hypersensitivities otherwise variegated and puzzling have the undernoted characteristics in common suggesting their unitarian origin

1 Etiology and pathogenesis otherwise unknown
2 Clinical manifestations usually suggest the operation of an infectious element
3 Failure to respond to antibiotic agents
4 Manifestations not palliated by antihistamines or adrenergens
5 Negative bacteriologic and serologic findings
6 In many a precedent history of upper respiratory infection
7 In many a *history of antecedent sensitivity reactions to food* drugs pollens etc

Pathogenesis The evolution and pathogenesis of tuberculin type hypersensitivity is suggested by study of phases of the rheumatic fever syndrome

EVOLUTION OF HYPERSENSITIVITY PHENOMENA IN RHEUMATIC FEVER

	Pathogenesis	Clinical Manifestations
Phase I	Introduction of antigen or allergen. Streptococcal invasion of tissue	Symptoms of upper respiratory infection intensity varying from subclinical to fulminant.
Phase II	Combined immunity and hypersensitivity response Development of antistreptolysin, perhaps of other immune bodies and of tuberculin hypersensitivity	Period of latency or incubation. Apparent recovery
Phase III	Reexposure to even minute amounts of streptococcal antigen (tuberculin type hypersensitivity)	Appearance of rheumatic syndrome with aseptic pyrexia leukocytosis increased sedimentation rate arthropathy cardiopathy dermatoses and sterile blood cultures
Phase IV	Spreading of hypersensitivity response to new allergen. Treatment with sulfonamide for example reproducing or intensifying tuberculin type hypersensitivity reactions	Intensification of symptoms with evidences of disturbances in collagen tissues (subcutaneous nodules) peripheral vessels (periarteritis nodosa) skin (purpuras erythemas etc) and heart (endocarditis myocarditis pericarditis etc)

The translation of these hypothetical considerations into terms of reality receives consideration in sections dealing with Prognosis (p 4174) and Therapy (p 4175)

ACUTE HISTAMINE TYPE AND CHRONIC TUBERCULIN TYPE ALLERGIC HYPERSENSITIVITIES

Similarities and Dissimilarities Because of the more obvious causal relationship between introduction of offending allergen and production of clinical manifestations acute histamine type allergic hypersensitivities have been more readily recognized and accepted than those due to chronic tuberculin type allergic hypersensitivity Despite obvious differences in clinical manifestations of acute and chronic syndromes each probably represents a stage in a single process each is the result of a perversion of mechanisms of body defense (p 4165) either may be produced by a single antigen such as heterologous serum which causes a transitory urticaria in one patient and a syndrome identical with periarteritis nodosa in another many patients with chronic hypersensitivity disorders give histories or evince evidences of precedent or concurrent histamine type hypersensitivities and finally many patients with acute histamine type hypersensitivities later in life develop the syndromes of chronic tuberculin type hypersensitivity such as rheumatoid arthritis diffuse lupus erythematosus etc

In *acute histamine type allergic hypersensitivity* symptoms occur relatively shortly after introduction of antigen injection of serum produces anaphylactic shock inhalation of pollen results in seasonal vaso

Disseminated lupus erythematosus (p 3399 and 4389)	Hemolytic treptococcus drugs (?) etc
Dermatomyo itis (p 3373)	?
Sterile dermatoses	Tuberculids (pp 3265 3299) leprids (p 273) syphilids (pp 334 3280 3285) dermatophytids (p 3299)
Specific skin test	Tuberculin (p 264) brucellergin (p 314) Frei test (p 471) trichinella (p 541) echinococcus test (p 1983) hi toplasmin test (p 504) coccidioidin test (p 499) actinomycin test (p 489) blastomycin test (p 493) Ducrey test (p 289)

Pathology The pathological changes in acute allergies are transitory and evanescent They consist essentially of edema and eosinophilia each of which is rapidly reversible

The pathology of human tuberculin type hypersensitivity has been studied by Rich who examined the tissues of patients who died shortly after the onset of systemic anaphylactic reactions due to administration of serum sulfonamide and the two antigens combined i e patients with serum sickness treated with sulfonamide

Irrespective of sensitizing agent Rich found diffuse lesions throughout the body These were characterized by swelling fragmentation and degeneration of collagen fibers focal circumferential infiltration of vessels by mononuclears and eosinophiles endothelial necrosis loss of the elastic layer endovascular thrombosis infarction of dependent ti sues aneurysm formation and rupture of necrotic segments of vessels

Lesions of *peripheral vessels* typified periarteritis nodosa *cardiac findings strongly suggested the rheumatic complex even to duplica*tion of Aschoff bodies and the Anitschkow myocyte *pulmonary lesions* revealed eosinophilic pneumonitis *cutaneous phenomena* included erythemas purpuras and lupus erythematosus *articular and periarticular changes* resembled those of rheumatic fever and rheumatoid arthritis and changes in the *central nervous system* suggested non suppurative encephalopathies as seen following administration of rabies vaccine and vaccine virus

The pathologic data become even more impressive since each simulated disease may present clinical manifestations identical with those regarded as specific to the others Thus *rheumatic fever* often is associated with arthropathy cardiopathy pneumonitis erythemas purpuras and chorea *periarteritis* with carditis pneumonitis glomerulonephritis purpuras urticarias and eosinophilia *diffuse lupus purpura* and *erythema multiforme with arthropathies cardiopathies and nephro*pathies *rheumatoid arthritis* with endocarditis subcutaneous nodules cleroderma and serous effusions

Lesions similar to those produced by hyper ensitivity to heterologous serums and bacteria also may be caused by sulfonamide iodide salicylate phenolphthalein dilantin acetylsalicylic acid and thiourea The insidious menace of tuberculin hypersensitivity looms darkly warning the therapist of the hazard of prescribing potential allergens for the hypersensitive

Fig 93 p 554) scratch and intradermal tests (p 557 Fig 34 p 263 Fig 94 p 555 and Fig 95 p 558) and the passive transfer reaction of Prausnitz Kustner (p 559)

The technics of these tests have been described in detail (p 555–561) but the attention of the reader is again drawn to the interpretation of findings (p 561) False negative and false positive responses may be obtained to the confusion of those who accept tests unequivocally without due consideration to clinical findings

Inferential Data Less scientific but at least equally valuable diagnosis of hypersensitivity is obtained from inferential data gleaned from history elimination tests and results of therapeutic trials

History The presence of hypersensitivity may be suggested by the history of repeated untoward responses after exposure to a particular offending allergen There would seem little need to add corroborative evidence to statements that the nose ran and became stuffed and the eyes teared annually at pollination time that ingestion of strawberries was consistently followed by hives that vomiting occurred immediately after ingestion of milk or milk products that exposure to horses produced shortness of breath and wheezing or that ingestion of chocolate was followed by headache

Elimination Tests Negative evidence of equal value may be obtained from elimination tests particularly in dealing with alimentary antigens which may shock the digestive tract but not the portion of skin that is tested (False negative test) Freedom from symptoms on Elimination Diets (p 562) and their reappearance on re umption of full diet or a meal inclusive of suspected offending allergen represent inferential diagnosis of the highest order of probity

Therapeutic Tests Finally inferential data may be obtained from therapeutic trials Palliation of presenting symptoms by antihistamines (p 4210) suggests that an attack of rhiniti for example is more likely a hypersensitivity response than an infective type of inflammatory reaction Many patients who state that they have recurrent colds obtain relief when given histamine antagonist indicating that the local inflammatory process in the nasal mucous membranes was more likely in the nature of an eosinophilic than a neutrophilic response

In chronic allergic sensitivities palliation by steroids possessing adrenocortical activity similarly suggests the nature of the tissue disturbance

Inferential Data versus Skin Tests It is our opinion that the value of inferential data exceeds that of skin reactions When inferential data are completely conclusive cutaneous reactions are gratuitous and not without danger (p 4164) When inferential data are positive and kin reactions negative the latter should be regarded as false Contrariwise in the pre ence of a positive cutaneous reaction but negative inferential data the skin test should be regarded as false positive

Course of Allergic Hypersensitivity

The course of acute histamine type hypersensitivity is dependent almost entirely on exposure to offending allergen In the pollinoses

motor rhinitis ingestion of sensitizing foods such as strawberries or fish produces urticaria or angioneurotic edema ingestion of cow s milk results in infantile eczema contact with poison ivy produces dermatitis venenata administration of certain drugs gives rise to cutaneous eruptions classified as dermatitis medicamentosa The clinical manifestations simulate those that may be produced by ingestion of histamine Specific antibody is demonstrable in the circulating fluid and can be transferred to experimental animals (Prausnitz Kustner reaction) Pathologic features almost invariably reversible include increased permeability of vessels exudation eosinophilic infiltration and spasm of smooth muscle The process relatively transitory is palliated by antihistamines and adrenergens and can be recreated by fresh exposure to offending antigen

Chronic tuberculin type hypersensitivity reactions are featured by incubation periods of variable duration separating causal phenomena and clinical manifestations Resultant symptoms are insidious in origin and more wide spread Pathologic features are noted principally in collagen interstitial tissues and vascular endothelium The dominant wandering cell is the monocyte rather than the eosinophile Specific *circulating antibody is difficult if not impossible to demonstrate* Passive transfer cannot be accomplished The symptoms are not duplicated by histamine injection symptomatic relief is not afforded by antihistamines or adrenergens but there is more than a glimmering of hope that palliation will be afforded by administration of steroids possessing adrenocortical activity

HISTAMINE TYPE *versus* **TUBERCULIN TYPE HYPERSENSITIVITY**

	Histamine type Hypersensitivity	Tuberculin type Hypersensitivity
Respon e	Immediate	Period of incubation
Specific antibody	Demonstrable	Not demonstrable
Precipitin test	Demonstrable	Not demonstrable
Passive transfer	Demonstrable	Not demonstrable
Local inflammation	Evanescent	Delayed insidious and progressive
Smooth muscle	Spasm	No response
Duplicated by histamine	Yes	No
Mechanism	*Liberation of histamine or* histamine like sub tances	*Unknown*
Relief from adrenergens and antihistamines	Yes	No
Relief from adrenal cortical hormone etc	Yes	Yes

Diagnosis of Allergic Hypersensitivities

The diagnosis of allergic hypersensitivities may be definitive or inferential In acute histamine type reactions definitive diagnosis more often prevails In chronic disorders recognition of the nature of the process is most always inferential

Definitive Diagnosis Definitive diagnosis of allergies rests on contact or patch tests (p 556 Fig 35 p 264) ophthalmic tests (p 556

latency or incubation This may last for days weeks years or decades only to erupt as in the Koch phenomenon (p 4168)

5 Hypersensitivity to a single antigen is not an unique phenomenon Hypersensitivity also may be exhibited to other substances including non bacterial antigens (products of industrial chemistry cosmetic or pharmacologic agents) Under these circumstances patient or physician may intensify or activate hypersensitivity responses by self medication or prescription of seemingly indicated medicaments such as salicylate iodide or sulfonamide

6 Infection of the hypersensitive patient with any other microorganism capable of producing tuberculin type hypersensitivity may activate manifestations due to the primarily sensitizing organi m Hence the prognosis of superimposed infection must be as guarded as the prognosis for reinfection by originally sensitizing allergen

Treatment of Allergic Hypersensitivities

With introduction of powerful histamine antagonists (p 4210) and of steroids possessing adrenocortical activity rea sessment of therapeutic principles in the management of allergic hypersensitivities (pp 563–565) is mandatory The discussion which follows is conducted more or less along broad general lines For specific information concerning practical management of definitively recognized allergic hyper ensitivities consult the following syndromes which are discussed in this volume

Anaphylactic Shock	Peri arteritis Nodosa
Atypical Verrucous Endocarditis	Physical Allergy
Bacterial Allergy	Pollen Allergy
Bronchial Asthma	Psychogenic Allergy
Contact Allergy	Purpuras
Dermatomyositis	Rheumatoid Arthritis
Disseminated Lupus Erythematosus	Rheumatic Fever
Drug Allergy	Serum Sickness
Erythema Multiforme	Thrombo angiitis Obliterans
Food Allergy	Urticaria and Angioneurotic Edema

General Principles of Treatment

Therapeutic objectives in the management of hypersensitivities include the following principles

1 conversion of hypersensitivity to active immunity
2 elimination of bacterial sensitizing agents
3 elimination of non bacterial ensitizing agents
4 substitution of a less sensitizing antigen for one known to be highly sensitizing
5 desensitization or hyposensitization
6 psychotherapy
7 palliation with adrenergens

exacerbations correspond to seasonal variations in the pollen content of atmospheric air for example Psychogenic factors probably cause quantitative variations in tissue response but the primary determinant is somatic

The courses of tuberculin type hypersensitivity syndromes vary as widely as the pathologic manifestations and as lists of potentially offending allergens The primary phase (as in rheumatic fever) may be subclinical or *fulminant under either circumstance the process may be* self limited intermittent or progressive Mild manifestations occur in those who compose the vast reservoir of unreported and unrecognized rheumatic fever the more seriously involved make up hospital populations upon which statistics of rheumatic fever are based (p 191) Tuberculin type hypersensitivity may be limited to a single shock organ such as the skin in uncomplicated purpuras but it is more likely that careful clinical study will reveal generalized changes in other organs of the body

Most characteristically tuberculin type sensitivities exhibit periods of exacerbation and remission Exacerbations undoubtedly are due to fresh exposure to offending allergen (as hemolytic streptococcus in rheumatic fever) or to another offending allergen (as sulfonamides in the treatment of serum sickness or iodides in fungus infections)

Prognosis in Allergic Hypersensitivities

Prognosis in acute allergies is most deceptive In fatal anaphylactic shock death of the patient may occur before the needle introducing offending allergen can be withdrawn by contrast the majority of acute histamine type allergies abate spontaneously leaving no chronic tissue manifestations of their presence

So greatly do imponderables outweigh ponderables in prognosticating tuberculin type hypersensitivity reactions that the draft of a definitive pronouncement would challenge even those astute lawyers who write the finely printed provisions of legal documents

The optimist who gives a favorable prognosis because of seemingly mild initial clinical manifestations may later be condemned as ignorant or negligent when the child with subclinical rheumatic fever after a decade is found to have a tight mitral stenosis On the other hand the more pessimistic physician (who views with alarm a seemingly fulminating streptococcal infection and predicts later invalidism and chronic illness) may be labeled an alarmist if the hypersensitivity reaction is sharply self limited to a single bout without chronic sequels

To guide the practitioner in prognosis of the *tuberculin type hypersensitivity* syndromes the following axioms are suggested

1 Intensity of Phase I gives no indication of the gravity of long term prognosis
2 Bacteriologic virulence of invading micro organisms gives no clue to the severity of tuberculin type hypersensitivity reactions
3 Intensity of local inflammatory reactions gives no indication of extent of long term damage to the patient
4 Guard against a sense of false security during the second phase of

this routine even in the face of seemingly discouraging progress

10 Since it is impossible at the time to determine whether any given upper respiratory infection constitutes Phase I of the tuberculin hypersensitivity reaction follow suggestion 1 in the treatment of each upper respiratory infection that occurs in each patient with a previous history of histamine type hypersensitivity tuberculin type hypersensitivity or any of their component syndromes

Elimination of Nonbacterial Sensitizing Agents Nonbacterial sensitizing agents appear provocative in many acute and chronic hypersensitivities The role of pollen food drugs serums etc in the pathogenesis of acute reactions has been previously described Less apparent has been the relationship of allergen to chronic syndromes However the work of Rich and others demonstrates that lesions of periarteritis nodo a rheumatoid arthritis rheumatic fever and glomerulonephritis may be produced experimentally as well as clinically by exposure of the sensitive to serums and drugs particularly sulfonamide salicylates iodide dilantin thiourea etc Attacks of paroxysmal hemoglobinuria may be induced in the sensitized syphilitic through the agency of cold damaged lens protein menaces the contralateral eye in sympathetic ophthalmia tobacco is suspect in thrombo-angiitis obliterans and solar energy appears noxious to the photosensitized patient with disseminated lupus erythematosus

In most instances elimination of pecific non bacterial sensitizing agents presents no formidable problem The patient with thrombo angiitis obliterans can get along very well without tobacco the photo ensitized can avoid solar energy and ufferers from paroxysmal hemoglobinuria can be protected against cold until such time as the underlying syphilis is controlled or eliminated Much more formidable is the problem in sympathetic ophthalmia Here it is necessary to perform enucleation of the injured eye in order to eliminate lens protein that menaces the healthy contralateral eye (p 1569)

Since hypersensitivity apparently spreads the patient with any allergic syndrome requires protection against all known offending allergens whether bacterial or non bacterial Thus it would seem reasonable to e chew common reactive substances such as pollens cosmetics chemicals sunlight and particularly tho e nonessential drugs which have been shown experimentally or clinically to be capable of inducing tuberculin type hypersensitivity There is no great problem attached to avoidance of phenolphthalein as a cathartic dilantin as an anti-epileptic or thio urea as an antithyroid preparation but the cases of iodide alicylate and sulfonamide require more elaborate con ideration

Iodide

Older clinicians for many years have warned against use of iodides in tuberculosis They observed instances in which administration of iodide was followed by exacerbation breakdown of caseous lesion and

8 prophylaxis and palliation with antihistamines
9 prophylaxis and/or palliation with adrenal cortical hormone pituitary adrenocorticotropic factor compound E etc

Conversion of Hypersensitivity to Active Immunity The recent suggestive relationship between adrenal cortical hormone and allergic hypersensitivities raise the first glimmering hopes for actual correction of those perversions of mechanisms of bodily defense responsible for production of these strange disorders Should it prove that cortical hormone or pituitary adrenocorticotropic factor determines cellular fixation or release of antibody the fundamental basis for hypersensitivities may be eliminated by administration of the specific endocrine product or its substitutes such as cortisone (p 4145)

Elimination of Bacterial Sensitizing Agents In certain hypersensitivities particularly chronic tuberculin type varieties (rheumatic fever purpura erythema multiforme etc) there is a definite history of precedent upper respiratory infection In rheumatic fever for example the invading sensitizing micro organism presumably is a hemolytic streptococcus Clearly then the prime aim of therapy is elimination of the offending bacterium

Using rheumatic fever as the prototype of tuberculin type hypersensitivities resulting from bacterial agents the following measures are advocated for prevention and treatment of tissue damage

1 In Phase I institute immediate treatment with large doses of penicillin (a feebly sensitizing antibiotic) to eliminate hemolytic *streptococci particularly from mucous membranes of upper* respiratory tract
2 Give concurrent antihistamine to prevent histamine type hypersensitivity reactions that occur in 10 to 15 per cent of sensitized patients who receive penicillin
3 Treat subclinical and mild infection as vigorously as the fulminant
4 Continue penicillin therapy well beyond the demonstrably infective period i e for at least two weeks after clinical manifestations have subsided
5 Continue antihistamine for at least two weeks longer than penicillin
6 When available supplement penicillin antihistamine therapy with adrenocortical hormone or one of its allied preparations such as cortisone (compound E)
7 In Phase II maintain the antistreptococcal attack by regular and repeated courses of penicillin Oral preparations may be prescribed for the first week in each month antihistamine may be given concurrently and for an additional week or approximately the first half of each month
8 During Phase II search for foci of infection particularly in the upper respiratory tract If these harbor hemolytic streptococci consider *surgical interference*
9 In Phase III with appearance of symptoms of rheumatic fever resume the routine of Phase I with clear understanding that procedures are prophylactic rather than palliative Persist with

this routine even in the face of seemingly discouraging progress

10 Since it is impossible at the time to determine whether any given upper respiratory infection constitutes Pha e I of the tuberculin hypersensitivity reaction follow suggestion 1 in the treatment of each upper respiratory infection that occurs in each patient with a previous history of histamine type hypersensitivity tuberculin type hyper-ensitivity or any of their component syndromes

Elimination of Nonbacterial Sensitizing Agents Nonbacterial sensitizing agents appear provocative in many acute and chronic hypersensitivities The role of pollen food drugs serums etc in the pathogenesis of acute reactions has been previously described Less apparent has been the relationship of allergen to chronic syndromes However the work of Rich and others demonstrates that lesions of periarteritis nodosa rheumatoid arthritis rheumatic fever and glomerulonephritis may be produced experimentally as well as clinically by exposure of the sensitive to serums and drugs particularly sulfonamide salicylates iodide dilantin thiourea etc Attacks of paroxysmal hemoglobinuria may be induced in the sensitized syphilitic through the agency of cold damaged lens protein menaces the contralateral eye in sympathetic ophthalmia tobacco is suspect in thrombo angiitis obliterans and solar energy appears noxious to the photosensitized patient with disseminated lupus erythematosus

In most instances elimination of specific non bacterial sensitizing agents presents no formidable problem The patient with thrombo angiitis obliterans can get along very well without tobacco the photo sensitized can avoid solar energy and sufferers from paroxysmal hemoglobinuria can be protected against cold until such time as the underlying syphilis is controlled or eliminated Much more formidable is the problem in sympathetic ophthalmia Here it is necessary to perform enucleation of the injured eye in order to eliminate lens protein that menaces the healthy contralateral eye (p 1569)

Since hypersensitivity apparently spreads the patient with any allergic syndrome requires protection against all known offending allergens whether bacterial or non bacterial Thus it would seem reasonable to eschew common reactive substances such as pollens cosmetics chemicals sunlight and particularly those nonessential drugs which have been shown experimentally or clinically to be capable of inducing tuberculin type hypersensitivity There is no great problem attached to avoidance of phenolphthalein as a cathartic dilantin as an anti epileptic or thio urea as an antithyroid preparation but the cases of iodide salicylate and sulfonamide require more elaborate consideration

Iodide

Older clinicians for many years have warned against use of iodides in tuberculosis They observed instances in which administration of iodide was followed by exacerbation breakdown of caseous lesions and

cavitation Similar intensification of clinical manifestations has been reported by physicians of wide experience in the management of deep fungus infections such as actinomycosis blastomycosis etc In these latter instances there is unanimity of opinion to defer iodide therapy until the patient has been desensitized with specific vaccine (p 4378)

In contrast to this frequently observed and generally credited menace of iodide therapy in the infections there is currently no comparable evidence to sustain the belief that iodides are possessed of significant antibiotic activity In consequence it would appear potentially hazardous and therapeutically unpromising to recommend iodide therapy in infection unless all other efforts have failed and the risk appeared warranted by the unfavorable course of the disease

Indications for iodide therapy in the arthropathies appear to be even less impressive than in the specific infections So far as is known iodides exert no consistently beneficial effect in any of the variou types of arthritis whether given by mouth inunction iontophoresis or vein In view of the su picion that rheumatic fever and rheumatoid arthritis are tuberculin type hypersensitivities it would appear poor judgment to administer a preparation that has so little therapeutic potential but *which is capable of eliciting tuberculin type hypersensitivity*

Salicylate

The salicylates have slightly more to recommend them therapeutically than the iodides Pharmacologically they possess palliative value allaying fever pain and swelling particularly in rheumatic fever Nevertheless for all the years that salicylates have been administered there has *never been sustained* evidence *that they have specific efficacy Whether* given in small or large doses or by whatever route most impartial observers agree that the ultimate course of rheumatic fever remains unchanged

In arriving at his decision whether to use or avoid salicylates in rheumatic fever the clinician *must* weigh immediate *symptomatic* relief against the potential of tuberculin type hypersensitivity It is our personal judgment to withhold the drug pending further investigation Defenders of continued salicylate therapy advance the argument that (1) symptomatic relief is prompt (2) salicylates may prevent hypersensitivity reactions experimentally as evidenced by experiences with typhoid vaccine and serum injections and (3) their participation in tuberculin type hypersensitivity reactions must be statistically very rare Nevertheless we prefer to palliate by less potentially hazardous means using hydrotherapy for antipyresis application of heat and occasional doses of demerol if necessary for analge ia

If the ca e for salicylate is assailable in rheumatic fever certainly it is even weaker in *rheumatoid arthritis and other arthropathies* In these conditions palliative effects are much less dramatic than in rheumatic fever and there is no claim whatsoever for specificity Therefore it is our judgment that it is wiser to palliate the complaints of rheumatoid arthritis and other *arthropathies with preparations having* lesser potential for sensitization than salicylate

Sulfonamide

The extraordinary antibiotic properties of sulfonamides are elsewhere discussed (p 4548) In this place attention is drawn to their sensitizing potentialities

The case against sulfonamides has been best summarized by Rich Harvey Lectures 1946

Death from serum sickness itself rarely if ever occurs However the use of sulfonamides in conjunction with foreign antibacterial serum can serve to prolong life sufficiently to permit the development of serum sickness in patients who will eventually die of their infection in spite of the treatment Furthermore shortly after the introduction of the sulfonamides in therapy it was pointed out that these drugs can produce a reaction altogether like that of serum sickness and further studies have shown that the sulfonamides can attach themselves to plasma protein and that the complex so formed can act as an antigen to sensitize the body anaphylactically to the sulfonamide radicle The continued administration of the sulfonamide after a sulfonamide hypersensitive reaction has appeared can markedly intensify the reaction and cause a fatal outcome As a result of these unfortunate accidents the widespread use of the sulfonamides greatly increased the opportunity to study the effects of the serum sickness type of anaphylactic reaction upon the tissues and in a study of a series of patients who died shortly after the onset of this type of hypersensitive reaction whether to foreign serum or to sulfonamides we found at autopsy typical fresh lesions of peri arteritis nodosa

A further confirmation of Rich s conclusions and observations are figures of the incidence of peri arteritis nodosa in autopsies done at the Johns Hopkins Hospital over a period of thirty years Between 1916 and 1936 there were performed 10 016 autopsies and six of these presented lesions of peri arteritis nodosa (0 06%) in the ten year period following introduction of sulfonamides (1936 to 1946) 5 207 autopsies were performed with 38 instances of peri arteritis nodosa (0 7%) a more than tenfold increase in the fatal incidence of this disorder

Were sulfonamide the only available remedy in the treatment of bacterial disease the hazard of tuberculin type hypersensitivity reaction would have to be overlooked Fortunately the physician may choose between sulfonamide and penicillin in the vast majority of infections Since there is as yet no evidence that penicillin has serious potential for chronic sensitization it should be substituted for sulfonamide whenever possible but particularly in the treatment of streptococcal diseases of infancy and childhood (p 4533)

Substitution of a Less Sensitizing Antigen In previous paragraphs which deal with the principle of elimination of potentially sensitizing preparations particularly drugs the policy of substitution of a less sensitizing antigen is illustrated Thus penicillin a feebly sensitizing antibiotic is preferred over sulfonamide which has demonstrably hypersensitizing properties insulin of beef origin may be replaced by insulin made from pigs etc

The sensitizing potential of sulfonamide is just one of several reasons for use of penicillin in each instance in which either may be indicated (p 4455) Avoidance of sulfonamide and choice of penicillin is mandatory under the following circumstances

1 infection is caused by a known sensitizing organism i e *hemolytic streptococcus*

2 the host is a sensitized individual with a history or clinical manifestations of histamine type or tuberculin type hypersensitivity syndromes

3 the host reports previous sensitizing phenomena as a result of sulfonamide administration serum injections etc

Desensitization or Hyposensitization Desensitization or hyposensitization in acute allergies using non bacterial antigens as in pollinosis is universally accepted (p 4477) Many attempts also have been made to increase host immunity and desensitize against specific proteins of *invasive micro organisms e g tuberculin luetin brucellergin actinomycin* blastomycin trichophytin etc

In contrast to reasonably successful pollen desensitization even enthusiasts for bacterial hyposensitization report inconsistent results *and warn against untoward reactions unless treatment is initiated and* maintained with sub reactive amounts of antigen

It is our current opinion that injections of bacterial antigen given for purposes of altering hypersensitivity reactions be reserved for those diseases for which we now possess no potent antibiotic This policy eliminates from the field of therapy luetin brucellergin trichophytin actinomycin etc Only in the management of diseases for which we do not have effective antibiotic therapy (such as blastomycosis for example) is vaccine desensitization worthy of consideration more for lack of something better to do than for anticipated results

Psychotherapy All hypersensitivities have psychogenic overtones just as are encountered in most recurrent crippling or progressive illnesses Only rarely is allergic hypersensitivity seemingly the direct result of psychic trauma

The compleat practitioner seeks to palliate psychogenic overtones particularly in crippling diseases such as rheumatoid arthritis or in frightening syndromes such as bronchial asthma When methods of non technical psychotherapy (p 1316) fail reference to the trained psychiatrist for formal therapy is seriously considered as a joint enterprise between specialist and practitioner

Palliation by Adrenergens Until introduction of antihistamines and steroids principal reliance in the treatment of acute hypersensitivities was placed on adrenergens (p 4158) Injections of epinephrine oral administration of ephedrine and sprays of other sympathomimetic amines (privine neosynephrin etc) afforded transitory but welcome relief

Availability of the new modalities has not by any means eliminated adrenergens from the therapeutic armamentarium Antihistamines and adrenergens are used *concurrently and synergistically* (p 4210) and

new adrenergic bronchodilators effective when given sublingually and orally have greatly simplified symptomatic management of bronchial asthma (p 4270)

Prophylaxis and Palliation by Antihistamines Antihistamines have demonstrable palliative effect in histamine type hypersensitivities They have no such clear-cut efficacy in tuberculin type hypersensitivities where they appear to alter presenting clinical manifestations little if at all

Despite lack of apparent symptomatic relief antihistamines merit prescription in tuberculin type hypersensitivities for potential long term prophylactic effects Since they do not have significant toxicity it is our personal opinion that they warrant use according to the under noted guiding principles

1 prescribe antihistamines routinely in the early phase of any clinical syndrome possibly caused by a potentially sensitizing micro-organism (p 4167)
2 prescribe antihistamine routinely in every infection of the hyper sensitive patient (p 4210)
3 prescribe antihistamines concurrently with therapeutic products that may possibly produce hypersensitivity reactions (serums iodide salicylate dilantin thiourea and antibiotics especially sulfonamide)

Prophylaxis and/or palliation with Adrenal Cortical Hormone Pituitary Adrenocorticotropic factor Compound E etc Interest in the treatment of tuberculin hypersensitivities has been stirred by new reports on the efficacy of adrenocortical hormone its pituitary adreno corticotropic factor and substitution steroid products such as cortisone or Compound E (17 hydroxy 11-dehydro corticosterone) Hench of the Mayo Clinic demonstrated extraordinary improvement in rheumatic fever and rheumatoid arthritis by daily injections of compound E This substance produced almost immediate symptomatic improvement of transitory duration although daily injections were required to prevent the patient from relapsing to pretreatment status

The theoretical importance of Hench s observation is of first magni tude since it forges a link between hypersensitivity and endocrine activity It has been long recognized that adrenal cortical hormone demonstrably increases output of antibody The new work suggests that it may also influence the *quality* of the response of defense mechanisms If it can be demonstrated that deficiency of adrenocortical secretion results in development of hypersensitivity and that contrariwise an adequate supply of adrenal cortical substance encourages mechanisms of active immunity then cortisone may not only palliate tuberculin type hypersensitivities but it should also prevent their occurrence It would be necessary only to demonstrate that adrenal cortical hormone influences parent cells to shed antibody (so that union between antigen and immune substance occurs extracellularly rather than intra cellularly) in order to implement the hope that prophylactic therapy is an impending achievement

AMEBACIDES

THERAPEUTICS OF AMEBACIDES

AMEBACIDAL ACTIVITY

Products	Intra intestinal	Extra intestinal	Comments
ALKALOIDS			
Ipecac U S P	Feeble	Feeble	Objectionable obsolete
Emetine hydrochloride U S P (p 529) Ampuls 1 cc — 65 mg (Abbott Lilly Merck P D Upjohn) Enteric coated emplets 20 mg (Lilly)	Fair	Excellent	91% of patients develop toxicity including local pain weakness precordial pain fall of blood pressure diarrhea nausea dyspnea, tachycardia dizziness head ache and changes in the electrocardiograms May be replaced by chloroquine or aureomycin
PENTAVALENT ARSENICALS (p 4230)			
Acetarsone N F (Stovarsol)	Good	Fair	Carbarsone mo t effectual and least toxic but may give arsenical reactions (p 122)
Carbarsone U S P	Good	Fair	
Phenarsone N N P (Aldarsone)	Good	Fair	
C C 914 C C 1037	Promising	Promising	Thioarsenites (p 4232) superior to their parent substance carbarsone and less toxic but not yet commercially available
OXYQUINOLINES (p 4443)			
Chiniofon U S P (Anayodin Yatren Quinoxyl) Diodoquin N N R Vioform N N R	Good	Fair	No significant toxicity but also less efficacious than originally believed Chiniofon and vioform may cause diarrhea on second or third days *Diodoquin preferred*
BISMUTH SUBCARBONATE (p 4255)	Poor	Poor	Obsolete
PARA AMINOBENZOIC ACID (PABA) N N R. (p 4445)	Promising	Promising	Effective for both intra and extra intestinal invasions Toxicity negligible
CHLOROQUINE N N R (Aralen)	Promising	Promising	Considered an effective substitute
PENICILLIN (p 4447)	Feeble	Feeble	Inve tigational Assist amebacides by elimination of econdary invaders
AUREOMYCIN (p 4241) CHLORAMPHENICOL (p 4279)	Promising	Promising	More effective clinically than in vitro Highly successful in limited series
WIA (Bismuth and Arsenic in organic combination)	Encouraging	——	Daily doses of 1 5 gm for 7 days to eliminate cy ts (Berberian)
BACITRACIN (p 4247)	Encouraging	——	40 to 160 000 units orally for twenty days

AMEBIASIS

[Amebic Dysentery]

Principles of Diagnosis and Treatment

1 An estimated 5 to 10 per cent of the population of North America harbor Endameba histolytica In urban communities the figure is con iderably below the average but among underprivileged dwellers in rural areas the percentage may approximate 20 or even 30 For the United States of America the numbers of citizens harboring E his tolytica are thought to be between 11 and 25 million

2 Most individuals with E histolytica in their stools are asymptomatic carriers the next largest group suffers from atypical clinical amebiasis later described only a very small number of the infected give evidences of classical amebic dysentery (p 523)

3 Whether carriers or sufferers from typical or atypical amebiasis the diagnosis rests on identification of trophozoites or cysts in stools (Fig 87 p 527) or in tissues (Fig 86 p 526) In stool specimens pathogenic E histolytica requires differentiation from fecal non pathogens such as E coli E nana I butschlii and B fragilis (Table 29 p 528)

4 At Tulane University School of Tropical Medicine the following routine is recommended for detection of E histolytica

(a) Examine at least three normally passed stools

(b) Give a saline cathartic the evening preceding stool collection Examine the first specimen passed the next morning

(c) Give two enemas each consisting of 1000 cc of physiologic saline solution Collect the last portions of the returns from the second enema and examine microscopically

(d) Following the second saline enema insert a sigmoidoscope and aspirate fecal material for microscopy

(e) Examine portions of the fresh specimens both stained and iodine-stained Place a representative fleck of feces or mucus thoroughly mixed with a drop of physiological saline on a clean microscopic slide Spread the film over an area of 2 inches Cover one half of the film with a cover glass To the other half add 1 drop of iodine and apply the cover glass Both halves of the slide are then examined microscopically

(f) If direct examination fails to disclose organism and the clinical suspicion of amebiasis is strong send a portion of the stool to the clinical pathologist for concentration and examination by such methods as the zinc sulfate centrifugal flotation technic and by preparing of fixed smears stained with iron and hematoxylin

(g) Asymptomatic carriers are detected only by stool examination For the most part their specimens contain only cysts However if these are not discovered and eliminated the carrier later may develop overt clinical manifestations but more significantly he may transmit the disease to others

(h) Next to carriers in numbers the largest group of patients infected with E histolytica present atypical and subclinical

manifestations Most commonly observed symptoms and signs are constipation mild diarrhea inability to gain weight colicky pains in the lower abdomen particularly the right lower quadrant localized tenderness over the colon nausea anorexia capricious appetite frontal headache myalgia backache disturbed nocturnal sleep diurnal somnolence poor memory asthenia vasomotor disturbances nervousness tachycardia easy fatigue and loss of ambition

(i) The classical textbook picture of amebic dysentery (p 524) is encountered least frequently of all

(j) Whether the patient is a carrier or presents subclinical or active clinical manifestations of amebiasis and whether overt manifestations are mild or severe energetic treatment is required The roster of amebacides includes alkaloids pentavalent arsenicals oxyquinolines bismuth para aminobenzoic acid chloroquine and the antibiotics penicillin aureomycin and chloramphenicol Some amebacides as illustrated by ipecac and emetine have greater postabsorptive extra intestinal activity than direct intra intestinal efficacy others like pentavalent arsenicals and oxyquinolines are more effective in their actions on organisms in the intestinal tract than on those that have passed the intestinal barrier

5 The efficacy of amebacides is enhanced by simultaneous use of antibacterial agents Seneca estimates the total bacterial count of the stools is increased fifty fold in amebiasis Coliform bacilli are increased thirty fold and the numbers of these fecal organisms protect amebae against the specific Conversely antibacterial agents permit amebacides to exert their full specific effect and hence appear synergistic though they have no great demonstrable amebacidal activity Thalamyd aureomycin and penicillin have been used as convenient non toxic adjuvants to non arsenical amebacides

6 There is no lack of effectual amebacides (p 1529 and p 4182) Rather is the practitioner confused by the multiplicity of available remedies and the fact that authorities differ as to their relative efficacy for the most part using several simultaneously or serially in their treatment of mass infections

7 The ideal amebacide should possess the following qualifications

(a) *Potent amebacidal activity for organisms within* the intestinal tract

(b) Potent amebacidal activity for extra intestinal invaders particularly those which have penetrated solid organs such as the liver

(c) Equally potent amebacidal activity against motile amebae trophozoites and cysts (Table 29 p 528)

(d) Minimum toxicity for the host

8 The more recently introduced amebacides give promise of partial fulfillment of these exacting requirements Any one of these may eventually replace emetine and pentavalent arsenicals for extra intestinal activity thus eliminating the hazard of host toxicity Similarly any or

all may be used in combination with equally non toxic oxyquinolines for more effective intra intestinal amebacidal effect The choices of the practitioner who deals with an occasional infection are those preparations which possess minimum threat of host toxicity

Practical Management

PROPHYLAXIS

Chloroquine (Aralen) Give 1 tablet of 250 mg thrice weekly (Chloroquine also is a malaria preventive)

Diodoquin Order 3 tablets each of 210 mg 3 times daily for three weeks Begin a few days before entering the endemic area Prefer diodoquin over arsenicals because of its lesser toxicity Of the oxyquinolines it is the preparation of choice since chiniofon (anayodin yatren quinoxyl) and vioform frequently cause diarrhea medicamentosa on the second or third treatment day

Since neither diodoquin nor chloroquine has significant toxicity the two preparations can be given *concurrently*

ACTIVE TREATMENT OF INTESTINAL MANIFESTATIONS (CARRIERS ASYMPTOMATIC OR MILD ATYPICAL MANIFESTATIONS OR OVERT ACUTE OR CHRONIC AMEBIC DYSENTERY)

Immediate Care

1 Start with least toxic amebacide such as diodoquin 3 tablets of 210 mg each thrice daily for 3 weeks or chloroquine (Aralen) 1 tablet of 100 mg 3 times daily for two to three weeks

2 Combine amebacide with antibacterial agent capable of reducing the numbers of fecal bacteria If expense is a factor use thalamyd in doses of 3 gm 3 times daily concurrently If the expense is not prohibitive use aureomycin in a daily dose approximating 30 mg per kilogram of body weight (2 gm or 8 capsules for average adult weighing 150 lbs) Give the daily dose in 4 equally divided portions

Continuing Care (Favorable Course)

1 If clinical symptoms subside and the stools become negative continue treatment for the full two or three weeks Then give the patient a treatment holiday of a similar period of time re examine stools and suggest a second course of therapy if needed Should the second course fail to clear stools follow directions for unfavorable course

Continuing Care (Unfavorable Course)

1 If symptoms persist stools remain positive or clinical or bacteriologic relapse is encountered substitute another amebacide for diodoquin or chloroquine Until C C 914 and C C 1037 (thioarsenites) are commercially available use carbarsone giving 1 tablet of 250 mg thrice daily for ten days

2 Continue oral anti infective agents for their effects on fecal contents using aureomycin or thalamyd

3 Supplement oral anti infective agents by deposits of penicillin Inject intramuscularly 600 000 units of procaine penicillin G in aqueous suspension or in oil with 2% aluminum monostearate Maintain penicillin level with injections every second or third day depending on the type of vehicle employed

4 Concurrently with penicillin give 200 mg of antihistamine using 4 daily doses of 50 mg each of pyribenzamine or benadryl to prevent hypersensitivity reactions

EXTRA INTESTINAL INFESTATION (PARTICULARLY LIVER ABSCESS)

Immediate Care

1 Inject 30 mg subcutaneously of emetine hydrochloride twice daily for eight to twelve days unless toxic symptoms develop sooner (p 529)

2 As an alternative providing the maximal concentration of emetine in the intestinal tract necessary to eradicate the parasite without producing toxic side effects order enteric coated enseals of emetine hydrochloride in 20 mg doses Provide for a total daily dose of 60 mg twice daily for twelve days Caution the patient to swallow the tablet whole

3 On the third day of emetine treatment if there are no toxic manifestations supplement alkaloid with an oxyquinoline preferably diodoquin in doses of 3 tablets of 210 mg each daily for three weeks

4 Concurrently with emetine-oxyquinoline give aureomycin or thalamyd orally for reduction in the numbers of fecal bacteria and deposit penicillin as previously described

Continuing Care (Unfavorable Course)

1 If the above described combined attack fails discontinue emetine and diodoquin

2 Substitute carbarsone in the dose of 250 mg tablets thrice daily for ten days

3 Continue oral administration of thalamyd or of aureomycin

4 Continue injections of penicillin

Continuing Care (Progressively Unfavorable Course)

1 For the amebacide substitute chloroquine using 1 tablet of 100 mg 3 times daily for two to three weeks or give para aminobenzoic acid 2 gm every 2 hours night and day for seven days to maintain a blood level of 30 to 60 mg per 100 cc of blood

2 Try retention enemas made by dissolving 2 gm of carbarsone in 200 cc of warm 2% sodium bicarbonate Administer amebacidal enema after cleansing alkaline enema every second night for ten days

3 Examine other members of the household to be sure that the patient is not being constantly re infected by a carrier within the household or among the food handlers

4 With failure of pharmacotherapy consider surgical drainage of feeding focus particularly in liver

ANALEPTICS

Analeptics are drugs capable of stimulating the central nervous system. They are used particularly for the treatment of acute barbiturate poisoning (p 4253)

Classification

In their exceedingly valuable report to the Council on Pharmacy and Chemistry Eckenhoff and associates divide analeptics into four categories (J A M A 139 780 1949)

1 Those with a primary stimulant action (picrotoxin metrazol nikethamide strychnine caffeine and atropine)

2 Those whose effects are reflex from one source or another (smelling salts whiskey brandy camphor alcohol ether cyanide sulfide nicotine and alpha lobeline)

3 Sympathomimetic drugs whose stimulant action on the central nervous system is disproportionately great in relation to that on the involuntary nervous system

4 Substances which increase the excitability of tissue by entering directly into a biochemical reaction (pyruvate succinate fumarate and components of vitamin B complex)

Therapeutics

Of the analeptics only picrotoxin metrazol nikethamide (coramine) alpha lobeline amphetamine d amphetamine (dexedrine) and desoxy ephedrine (methedrine) merit consideration These preparations are compared in the chart which follows (p 4188)

Because of their relative toxicity consideration need not be given strychnine caffeine atropine cyanide sulfides and nicotine Because of their relatively feeble action smelling salts whiskey brandy camphor alcohol sympathomimetic amines (other than those above mentioned) pyruvate succinate fumarate and components of vitamin B complex may be discarded

ANAPHYLACTIC SHOCK

Most instances of anaphylactic hypersensitivity occur when a biological is injected by the physician with therapeutic intent. Those practitioners who have unwittingly induced or even witnessed this violent and occasionally lethal treatment reaction certainly will not wish to short-cut the admittedly cumbersome routines which follow

Of therapeutic principles listed in the management of hypersensitivity reactions (p 4175) the practitioner is limited to desensitization or hyposensitization and palliation and prophylaxis with adrenergen and antihistamines (p 4210)

Determination of Degree of Hypersensitivity Before introduction of any biological even in test doses the patient is questioned relative to

ANALEPTICS

Drug	Available Products	Initial Dose	Succeeding Doses	Notes
Picrotoxin U S P	20 cc vials 1 cc — 3 mg For intravenous use	2 cc	3 to 5 cc (9 to 15 mg) at 15-30 minute inter vals	Most potent analeptic agent for treating barbiturate depre sion Latent period of ten to thirty minutes makes metrazol preferable for immediate treatment of poi oning by rapidly acting barbiturates and requires that ucceeding doses be delayed for at least twenty to thirty minutes to avo d accumulation leading to convulsions
Metrazol (Pentylene tet razol) N N R	Ampuls 1 or 3 cc 1 cc — 100 mg For subcutaneous intramus cular or intravenous in jection	1 to 3 cc	1 to 3 cc	Valuable analeptic but inferior to picrotoxin in potency Maximum effect immediately follows intra venous injection favoring its use over picrotoxin in respiratory depres ions due to short acting barbitu rates Requires frequent introduction since duration of action is brief May be combined with picrotoxin using metrazol for immediate effect and picrotoxin for delayed effect
Nikethamide (Coramine) N N P	Ampuls 1 5 2 or 5 cc 1 cc — 250 mg For subcutaneous intramus cular or intravenous in jection	3 cc	5 to 10 cc every five minutes if nece sary	Definitely inferior to picrotoxin or metrazol as an an aleptic agent
Amphetamine Sulfate (Benzedrine Sulfate) N N P	Tablets 5 and 10 mg Improvise solution by dissolving 10 mg in 1 cc of physiologic o dium chloride	1 cc	1 cc at 30 minute inter vals	Action immediate but may cau e sympathomimetic side effects such as elevation of blood pressure etc Prefer metrazol for immediate action and picrotoxin for delayed effect
Methamphetamine Hy drochloride (Desoxyn Hydrochloride) N N R	As Amphetamine Sul fate			
Alpha Lobeline	Ampuls 1 cc — 3 2 mg (infants) or 9 7 mg (adults)	1 cc conta ning 3 2 mg for infants and 1 cc containing 9 7 mg for the adults subcutaneou ly	Every thirty minutes if nece sary	Action uncertain and usually followed by a period of depre sion Not recommended in view of the avail ability of other better analeptic drugs

previous hypersensitivity reactions Inquiry is made concerning personal and familial evidences of common allergic syndromes (hay fever food or drug idiosyncrasy bronchial asthma etc) previous injections of serum and the nature of previous responses to injected biologicals Not until these questions have been answered is it safe to proceed with cutaneous testing much less therapeutic injections of serum or other potential allergens

Terminology

1 By *hypersensitivity* is meant the presence of any local or constitutional allergic hypersensitivity reaction whether acute histamine type or chronic tuberculin type

2 *Negative sensitivity* implies neither personal nor familial history of allergies and no previous record of injection of biologicals for diagnosis or therapy

3 *Presumptive sensitivity* is assumed when there is a history of personal or familial allergy and/or of previous injection of a biological

4 *Probable sensitivity* exists in the presence of any presumptive evidence with an additional history of hypersensitivity to serum testing

5 *Positive sensitivity* implies the presence of all probable evidences plus the history of a hypersensitivity reaction to previous therapeutic serum injection

Cutaneous Tests

After eliciting the history for rough estimation of the degree of hypersensitivity the following procedure is suggested for skin testing

NEGATIVE HISTORY

Time	Procedure	Negative Response	Positive Response
0 0	Scratch test, 1 10 dilution of serum, etc (p 557)	Proceed as per protocol	Regard as presumptive Proceed as below
0 20	Intracutaneous test (p 557) 1 1000 dilution	Proceed as per protocol	Desensitize (p 4191)
0 40	Intracutaneous test, 1 100 dilution	Proceed as per protocol	Desensitize
0 60	Intracutaneous test, 1 10 dilution	Inject without desensitization as per directions (p 4190)	Desensitize

PRESUMPTIVE HISTORY

Time	Procedure	Negative Response	Positive Response
0 0	Scratch test 1 10	Proceed as per protocol	Desensitize (p 4191)
0 15	Intracutaneous 1 10 000	Proceed as per protocol	Desensitize
0 30	Intracutaneous 1 1 000	Proceed as per protocol	Desensitize
0 45	Intracutaneous 1 100	Proceed as per protocol	Desensitize
0 60	Intracutaneous 1 10	Inject without desensitization as per direction (p 4190)	Desensitize

PROBABLE OR POSITIVE SENSITIVITY

1 Avoid injection, if possible
2 If patient has received previous specific antitoxin, as for example tetanus or diph

theria substitute fluid alum precipitated toxoid in a booster dose of 0 1 cc (p 4364)
3 If antibiotic alone may be effectual withhold antiserum unle s there is desperation need (p 4564)
4 If compelled to give antiserum proceed with desensitization as indicated below

Therapeutic Procedure

The routines which follow are time consuming and laborious Never theless the tragedy of anaphylactic death more frequently encoun tered than generally reputed warrants hyper precaution with each and every injection of a potential allergen

SERUM INJECTIONS FOR THOSE WITH NEGATIVE OR PRESUMPTIVE HISTORIES OF HYPERSENSITIVITY AND COMPLETELY NEGATIVE CUTANEOUS TESTS

1 At least thirty minutes before planned therapeutic injection give prophylactic intramuscular or intravenous injection of 2 to 5 cc of diphenhydramine hydrochloride (benadryl) Each cc contains 10 mg of anti histamine (p 4210)

2 If for some reason injectable antihistamine is not available sub stitute oral dose of 100 mg of pyribenzamine benadryl or any other antihistamine (p 4212)

3 Refill the syringe with benadryl solution for active treatment of any hypersensitivity reaction which may develop despite negative his tory negative tests and prophylactic use of antihistamine

4 Prepare a second syringe with adrenergen (2 cc of epinephrine hydrochloride 1 1000) for subcutaneous or intramuscular injection with benadryl if hypersensitivity is encountered

5 Having taken these precautions inject undiluted specific anti serum intramuscularly *If intravenous administration is indicated* dilute to 200 cc with sterile distilled water or isotonic saline solution and give slowly by intravenous drip (p 3775) To the serum saline mixture may be added 2 to 5 cc of 1% benadryl and/or 1 cc 1 1000 epinephrine

6 If there is the slightest suspicion of a hypersensitivity reaction interrupt injection and repeat intramuscular or intravenous injection of benadryl with subcutaneous or intramuscular injection of epinephrine

7 At the end of an hour if there has been no evidence of hyper sensitivity order oral doses of 50 mg of benadryl or pyribenzamine four times daily for two weeks for prevention of serum sickness (p 4519)

SERUM INJECTIONS FOR PATIENTS REQUIRING DESENSITIZATION

It is reasonably safe for the practitioner to give serum injections in his office or in the home of the patient with a negative or a presump tive history of hypersensitivity and completely negative cutaneous tests However it is inadvisable to introduce biologicals into those with proba ble or positive hypersensitivity except under hospital supervision Under the latter circumstance this procedure is advised

1 Inject intramuscularly or intravenously 2 to 5 cc of diphenhy dramine hydrochloride (benadryl) Each cc contains 10 mg of anti histamine

2 Substitute 100 mg of pyribenzamine benadryl or other anti histamine orally if for some rea on injectable product cannot be given

3 Refill benadryl syringe with another 5 cc of antihistamine to pre pare for any hypersensitivity reaction that may develop during or fol lowing desensitization or therapeutic injection of serum despite all precautions

4 Prepare a second syringe with 2 cc of adrenergen (epinephrine hydrochloride [1 1000]) for subcutaneous or intramuscular injection to supplement benadryl if hypersensitivity is encountered

5 Follow the undernoted schedule for desensitization by subcu taneous injection before administration of the full therapeutic dose

SCHEDULE FOR DESENSITIZATION

Time H M	Dilution	Volume in cc	No Reaction	Reaction
0 0	1 1000	0 1	As per protocol	Repeat after 30 minutes
0 15	1 1000	0 2		
0 30	1 1000	0 3		
0 45	1 1000	0 5		
1 0	1 1000	1 0		
1 15	1 100	0 1		
1 30	1 100	0 2		
1 45	1 100	0 5		
2 0	1 100	1 0		
2 15	1 10	0 1		
2 30	1 10	0 2		
2 45	1 10	0 5		
3 0	1 10	1 0		
3 15	Undiluted	0 1		
3 30		0 2		
3 45		0 5		
4 0		1 0		

If the reaction is mild to moderate treat with antihistamine plus adrenergen after an interval of 30 minutes resume desensitization repeating last asymptomatic dose If reaction is severe or repeated consider abandonment of serum therapy

6 After desensitization has been completed without reaction repeat injection of benadryl as in 1

7 Half hour later inject intramuscularly remainder of required unitage of antiserum at one dose

8 Remain with patient for at least one hour after serum has been introduced

9 Immediately thereafter start oral doses of antihistamine pyribenza mine benadryl etc and continue for fourteen days after last injection to prevent serum sickness

10 If it becomes necessary to repeat antiserum above procedure must be followed each time since hypersensitivity may develop or alter on short notice

ANDROGENS

Androgens are steroid compound. exhibiting properties of male sex hormones (p 2484)

Available Preparations

Innumerable androgenic substances have been naturally obtained and synthetically derived Of these the most potent is testosterone available as the following council approved preparations

Methyl testosterone U S P Tablets (Rare Chemicals) 10 and 20 mg About one third as effective a. intramuscular injection

Testosterone propionate U S P (Rare Chemicals) Ampuls of 5 10 25 and 50 mg in 1 cc of sesame oil

Metandren Linguets (Ciba) 5 and 10 mg for oral absorption Almost as effective as intramuscular injection if held for 30 to 50 minutes

General Principles of Pharmacology and Therapeutics

1 Effects of androgenic activity on any given organism are dependent on prevailing hormonal equilibrium in the given patient at the given time Thus androgen stimulates spermatogenesis in prepuberal hypogonadism but may inhibit this function in older patients with relatively normal hormonal equilibrium

2 Since variables in hormonal equilibrium are immeasurable and imponderable indications for androgenic therapy cannot be established by rote Male hormone therapy is a clinical experiment requiring careful preliminary analysis and even more careful observation during and after exhibition of the steroid

3 Most generalizations and therapeutic claims particularly those of enthusiasts are based on effects noted in castrated animals and in the rarely encountered clinical syndrome of prepuberal hypogonadism (p 2413) Under either of these circumstances it is quite correct to report such changes as increase in growth body weight strength vigor muscle mass size of genitals libido sexuality and spermatogenesis It is misleading and inaccurate to intimate that similar effects may be anticipated in patients not afflicted with gross hormonal deficiency

4 *Failure to indicate differences in host responses to hormonal* therapy has created considerable confusion Understandably the practitioner has difficulty reconciling the glittering reports of enthusiasts with his less miraculous personal experiences

5 In the prescription or administration of androgen to the older male first consideration must be granted potential carcinogenic activity relative particularly to the prostate The specter of this tragic manifestation has made us unwilling to use androgen unless indications are crystal clear and other therapeutic endeavors have been meticulously tried and found wanting

6 In the female first consideration must be accorded the cosmetic side effects of hirsuties and acne Whereas it is generally true that arrhenomimetic activity is related to dose and rarely occurs with less

than 500 mg of testosterone propionate per menstrual cycle certain phenomena (notably hirsuties and acne vulgaris) may be intensified in those who already have a pre treatment tendency to hairiness and the dermatosis

7 Finally evaluation of therapeutic results with androgen is com plicated by psychotherapeutic influences In the minds of the laity male sex hormone symbolizes vigor libido sexuality and genitalism Actually most effective therapeutics with androgens is accomplished in the non sexual sphere as indicated in the tables

ANDROGYNOUS EFFECTS OF ANDROGENS

Without regard to sex, androgen therapy is recommended in a variety of clinical *conditions mostly endocrinopathies The practitioner will note paradoxical indications* which usually depend on the state of hormonal equilibrium at the time of institution of therapy i e in anterior pituitary disorders to inhibit secretion in hyperpituitarism and again to stimulate the output of growth factor in dwarfism

Acromegaly (p 1156)
To suppress hypersecretion of anterior pituitary growth factor

Adiposo-Genital Syndrome (Froehlich syndrome p 1166)
For stimulation of anterior pituitary growth hormone Use only with bilatera intra-abdominal cryptorchism Otherwise give gonadotropic hormone

Adrenocortical Deficiency (Addison s Disease) (p 1276 4159)
To stimulate output of adrenal cortical hormone

Angina Pectoris (p 893) **Arteriosclerosis Coronary Insufficiency and Sclerosis**
On the basis of increased blood volume and increased tonus of cardiac muscu lature following androgen therapy in castrated animals administration of male sex hormone has been suggested in the treatment of angina pectoris Inasmuch as the normal adult, in hormonal equilibrium does not respond as the eunuchoid experimental animal reported favorable results are probably psychotherapeutic

Dwarfism (p 693)
For stimulation of anterior pituitary growth hormone

Giantism Hyperpituitarism
See Acromegaly

Hypopituitarism
See Dwarfism and Adiposogenital Syndrome

Peptic Ulcer (p 1780)
Irrational indication on the paradoxical basis that peptic ulceration is infinitely more common in the male Re ults are due presumably to psychotherapy or spontaneous healing

Peripheral Vascular Disease
See Angina Pectoris

Prematurity
In prepuberal hypogonadism there are retentions of nitrogen sodium chlo ride and water increa e of muscle mass due to protein anabolism and an elevation of the basal metabolic rate These effects cannot be expected in the adult with relatively normal hormonal equilibrium but may occur in premature infants

Rheumatoid Arthritis (p 2925 and 4502)
As substitute for less easily available cortisone (adreno cortical hormone)

ANDROGEN THERAPY IN THE MALE

Climacteric (p 2414)
Lurking hazard of prostatic carcinogenesis narrows use to those with severe and intractable symptoms as observed in very rare instances in our experi ence If given use cocktail consisting of androgen and estrogen in the ratio

of 10 mg of the former to 0 5 mg of diethylstilbestrol Inject 75 mg testosterone weekly

Infertility Sterility

Of value only in the rare instance of sterility or infertility due to primary hypogonadism (p 2419)

Hypogonadism

Specific replacement therapy in prepuberal primary hypogonadism (Figs 577 p 2415 and p 2416) Prefer anterior pituitary gonadotropic hormone in secondary hypogonadism (Fig 578 p 2416) and particularly in cryptorchism (Fig 581 p 2425 and p 2423)

Impotence

Increase of libido only where impotence is the result of primary hypogonadism (p 2109)

Mumps (p 4418)

For prevention and treatment of orchitis

Prostatic hypertrophy (p 2445)

Potentially carcinogenic

Weight Gain

Only in those with primary hypogonadism

ANDROGEN THERAPY IN THE FEMALE

Salmon (Progress in Gynecology 1946) states that androgen effects in the female may be divided into 4 sequential phases induced by increasing dosage levels of hormone (1) Estrogen attenuation and neutralization (50 to 150 mg per cycle) (2) Ovarian inhibition (200 to 250 mg per cycle) (3) pituitary inhibition (350 to 400 mg per cycle and (4) arrhenomimesis (500 mg plus per cycle)

Anticarcinogenesis

Particularly in metastatic malignancy of the breast (p 2581 4326)

Breast Engorgement

Prefer use of ammonium chloride

Breast

See anticarcinogenesis and lactation

Dysmenorrhea

Moderate doses up to 200 mg in divided doses per menstrual cycle may be effective in primary dysmenorrhea (p 2561)

Dysovulation

Small doses up to 100 mg in 4 equally divided amounts administered during pre ovulatory phase of cycle for two succes ive months may be effective in preventing mittelschmerz (midmenstrual pain)

Endometriosis

In early cases with history of severe premenstrual or intermenstrual pain but without positive findings where conservative surgical measures are employed to preserve child bearing capacity or ovarian function for advanced ca es in which radical surgery is indicated but must be postponed for medical or social reasons pre operatively in advanced cases particularly with bowel involvement

Frigidity Genital Underdevelopment (Clitoris)

Small doses up to 150 mg per men trual cycle may produce enlargement with increased libido and more satisfactory orgasm

Fibroids

Particularly associated with menorrhagia

Homosexuality Lesbianism

Of no value other than psychotherapeutic

Lactation

For suppression of anterior pituitary lactogenic factor following pregnancy Two daily intramuscular doses each of 25 mg preceding onset of lactation

Mastalgia

See Breast engorgement.

Meno-Metrorrhagia

If malignancy is excluded consider symptomatic use Inject 150 mg during first two weeks of cycle (p 2557)

Menopause
Anticarcinogenic effect relative to the breast Use in preference to estrogen.
Menstruation
May be inhibited through suppression of anterior pituitary gonadotropic factor
Mittelschmerz
See Dysovulation
Ovulation
May be suppressed through secondary effect on anterior pituitary gonadotropic hormone
Premenstrual Tension
Prefer Ammonium chloride

ANTABUS

Tetraethylthiuran disulfide marketed as antabus is a white or slightly yellow powder insoluble in water Antabus is relatively non toxic to man in single daily doses of 3 gm or of repeated daily do es of 0 25 to 1 gm provided that alcohol is not ingested

Available Preparations

Antabus (Ayerst McKenna and Harrison) Tablets 0 5 gm
Antabus has not yet been licensed for general distribution It is still (1950) in the stage of clinical investigation under the auspices of governmental authorities in the United States and Canada

Pharmacology

Human beings not exposed to alcohol reveal no untoward effects from antabus taken in single doses of 3 gm or daily doses of 0 25 to 1 gm for several months Neither subjective nor objective manifestations are observed other than fatigability an occasional instance of decreased sexual potency and somnolence Examinations of blood urine renal and hepatic functions and electrocardiograms show no abnormalities attributable to the drug during continued treatment
Elimination of antabus from the body is slow Ingestion of 1 5 gm can be traced for seven to eight days after introduction

Therapeutics

When the human subject has taken as little as 1 gm of antabus within the previous twelve hours intake of alcohol produces a facial sensation of heat within five to fifteen minutes A few moments later there is intense vasodilatation of face and neck the whole area appearing a purple red Some patients reveal vasodilatation as well on other parts of chest and arms At the same time there is a striking vasodilatation of scleras with slight edema of the loose connective tissue under the lower eyelids
Accompanying the initial vasodilatation there is a decided increase in skin temperature The pulse rate rises to 120 to 140 beats per minute blood pre sure is unaltered or slightly depressed cardiac output is

increased about 50 per cent pulmonary ventilation is increased with a corresponding decrease in alveolar carbon dioxide

Sometimes nausea is noted thirty to sixty minutes after consumption of alcohol With the onset of nausea flushing is replaced by pallor and there is a con iderable fall in systolic and diastolic blood pressures Copious vomiting may occur with or without precedent nausea

At the time of nausea there is an intense feeling of discomfort with pulsating headache palpitation subjective dyspnea a sensation of con striction in the neck as though the collar had become too tight a feeling of a premature hangover tenesmus diarrhea and a garlic taste and odor to the breath

With larger doses of alcohol in some patients there is in addition dizziness somnolence and unconsciousness for as long as a half hour Still larger doses particularly in more sensitive patients may result in toxic symptoms including dermatoses peripheral circulatory collapse with absent pulse convulsions amnesia hemiparesis and even death

Antabus sensitization to alcohol is associated with elevation of blood acetaldehyde levels acetonuria and an intense characteristic smell of acetone on the expired breath

Although the use of antabus in the treatment of alcoholism is still in the experimental phase the original Danish inve tigators Hald Jacobsen and Martensen Larsen have already reported on the treatment of 550 patients As modified by Canadian investigators Gelbman and Epstein the following routine has been established for use only by experienced investigators with facilities for the treatment of severe untoward reactions

1 Before ingestion of antabus insist on a period of at least forty eight hours and preferably of one week of sobriety
2 In the presence of a relative friend social worker or member of Alcoholics Anonymous explain the method of treatment to the patient preferably with a group of others similarly afflicted Allocate to each patient 9 tablets each of 0 5 gm to total 4 5 gm
3 Have patient swallow 4 tablets immediately under observation of physician and remaining members of the group
4 If patient is ambulatory have responsible friend or associate see that 3 tablets are taken the next morning
5 Again in the presence of a friend or associated investigator have patient swallow 2 tablets on the morning of the second day
6 On the afternoon of the second day patient with attendants comes to the office or hospital of the chief investigator and brings along his favorite form of alcohol
7 In the presence of the physician and other members of the group the patient pours out for himself 2 to 6 ounces of hard liquor or 1 quart of beer and is asked to drink in his normal fashion
8 On first appearance of symptoms of sensitization to alcohol drink ing is discontinued
9 Thereafter the patient is given an antabus maintenance dose of 0 25 to 0 75 gm daily The amount is adjusted so that flushing occurs after ingestion of 1 teaspoonful of alcohol

10 Under guidance of friends relatives social workers or com panions in Alcoholics Anonymous patient is observed daily to be sure that tablets are taken During this time necessary psy chotherapy is introduced Patients observed for six months or more following treatment with antabus enjoyed social recovery in 52 per cent and marked improvement in 19 per cent Only 16 per cent were reported as unchanged and these for the most part were individuals with pronounced mental symptoms before therapy was instituted

11 Whereas Danish workers report no absolute contraindications to Antabus therapy in alcoholism extreme precautions would cer tainly appear warranted in those with cardiova cular disturbances renal or hepatic insufficiency epilepsy diabetes and other chronic diseases

12 For protection of ambulatory patients the Canadian investigators give cards to patients which read 'The bearer of this card is taking Antabus The drug alone is harmless When combined with alcohol symptoms of marked flushing perspiration red ness of the eyeballs difficulty in breathing odor of acetone on the breath palpitations vomiting and low blood pressure will be marked If such a reaction occurs and is severe please call the hospital and get in touch with the doctor on call at the department

ANTHELMINTICS

The more highly organized invaders of the human body are less susceptible to anti infective agents than lowlier bacteria amebas and protozoa Indications for anthelmintics are determined by the nature of the infesting organism and by the extent to which host tissues have been invaded Fortunately most helminths remain wholly intra intestinal where they are vulnerable to oral medication Those which penetrate the barrier of the intestinal mucosa (particularly flukes) and those which are deposited subcutaneously by vectors (such as filaria) require medicaments which possess post ab orptive activity

Whether prescribed for pre or post absorptive effects most anthel mintics are potentially toxic to the host In his choice of drug the practi tioner selects the least hazardous preparation reserving more toxic products for refractory or recurrent infestations as indicated in the following table

ANTHELMINTICS

Preparation	Indication	Toxicity
Aspidium U S P (Male Fern) Oleoresin of	Teniasis	Moderate (p 1895)
Atabrine see *Quinacrine*		
Betanaphthol U S P	Uncinariasis and intestinal dis tomiasis	Negligible

ANTHELMINTICS—Continued

Preparation	Indication	Toxicity
Carbon Tetrachloride N F	Superseded by less toxic tetra chlorethylene in uncinariasis and intestinal di tomia is U e only for refractory infe tations	Considerable (p 1897)
Chenopodium U S P (American Worm Seed) Oil of	Ascariasis and trichuriasis	Considerable (p 1896)
Diphenan	Enterobiasis	Negligible
Emetine hydrochloric acid U S P	Pulmonary Paragonimiasis	Considerable (p 520)
Gentian Violet N N R (Methylbiosaniline)	Enterobiasis (Pinworm) and strongyloidiasis	Negligible
Hetrazan	Fir t choice in filariasis May re place hexylresorcinol as first choice in ascariasis Try also in trichinosis	Negligible
Hexylresorcinol U S P (Caprokol Crystoid)	Ascariasis intestinal distomiasis trichuriasis enterobiasis unci nariasis and teniasis	Negligible
Leche de higueron (Ficus Laurifolia)	Where available and fresh in ascariasis trichuriasis and en terobiasis Not obtainable in U S A	Moderate
Pelletierine Tannate U S P	Teniasis	Considerable (p 1896)
Phenothiazine	Enterobiasis	Moderate
Quinacrine	Teniasis	Negligible
Santonin U S P	Ascariasis	Considerable (p 1896)
Tetrachlorethylene N F	Uncinariasis intestinal disto miasis and trichuriasis	Minor (p 1895) Contra indicated in presence of ascariasis
Thymol U S P	Uncinariasis	Considerable (p 1897)

ANTHRAX

[Malignant Pustule Woolsorter s Disease]

Principles of Treatment

1 Prior to introduction of antibiotics cutaneous anthrax (malignant pustule) carried a mortality of 20 to 25 per cent (Fig 42 p 293) With pulmonary involvement (woolsorter s disease p 2190) recovery was unusual if it occurred at all

2 Because of its properties of encapsulation and sporulation B anthracis is resistant to antibiotics unless given in high doses With adequate and sustained levels however the organism exhibits sensi tivity to penicillin sulfonamide streptomycin aureomycin and chloram phenicol

3 The combination of high mortality and organism resistance demands vigorous combined treatment

4 Heterologous anti anthrax serum is no longer Council approved nor commercially available It was not antitoxic its antibacterial potency was feeble at best and it imposed the threat of hypersensitivity reactions

5 In view of the efficacy of antibiotic treatment surgical excision of the malignant pustule may be deferred Instrumentation of the wound carries greater threat for dissemination of invading organisms than is warranted by potential benefits resulting from attempted eradication of the feeding focus

Practical Management

Immediate Care

1 Transfer the patient to a hospital for isolation and professional nursing care

2 Cover wound with sterilized petrolatum Warn attendants to avoid contamination of their persons instruments or apparatus with this highly virulent organism

3 Inject intramuscularly 500 000 units of crystalline penicillin G in aqueous solution for immediate priming effect Simultaneously deposit 600 000 units of procaine penicillin G in oil with 2% aluminum monostearate for maintenance of maximum therapeutic levels

4 *Administer orally a loading dose of 2 gm each of sulfadiazine and* sulfamerazine with 4 gm of bicarbonate of soda If the patient suffers gastric intolerance or is unable to swallow tablets inject intravenously 2 5 gm. each of sodium sulfadiazine and sodium sulfamerazine in 200 to 500 cc of molar lactate or physiologic saline solution (p 4546)

5 If stomach is tolerant supplement penicillin sulfonamide by oral administration of a priming dose of 4 gm of aureomycin or chloram phenicol preferably the latter which has a lesser tendency to produce gastric irritation Substitute 2 gm of streptomycin intramuscularly if the stomach is intolerant

6 Initiate prophylactic antihistamine therapy Prescribe 50 mg of pyribenzamine or benadryl four times daily If the patient is unable to swallow inject 5 cc of 1% benadryl intramuscularly

Continuing Care (Favorable Course)

1 Maintain penicillin levels by intramuscular injections at 3 4 6 or 8 hour intervals of 300 000 to 600 000 units of procaine penicillin Gl in oil with 2% aluminum monostearate being guided by the clinica course and the patient s apparent response to therapy

2 Maintain sulfonamide levels by oral administration of 0 5 gm each of sulfadiazine and sulfamerazine at 4 or 6 hour intervals depend ing on patient response to treatment and evidences of toxicity (p 4541) If the stomach is still intolerant inject intravenously 2 5 gm each of odium sulfadiazine and sodium sulfamerazine preferably in 200 to 500 cc of molar lactate or physiologic aline Repeat every eight to twelve hours as indicated

3 Maintain antibiotic levels by oral administration of 0 5 gm of aureomycin or chloramphenicol every three or four hours If ga.tric intolerance persists inject intramuscularly 0 5 gm streptomycin every six to eight hours as required

4 Continue use of antihistamine in a total daily oral dose of 200 mg

5 Unless toxic .ymptoms develop continue triple antibiotic attack

with penicillin sulfonamide and streptomycin for a minimum period of ten days Continue antihistamine for another two weeks

Continuing Care (Unfavorable Course)

1 Increase penicillin levels by raising each dose to 600 000 to 1 000 000 units procaine penicillin G Decrease intervals to every three or four hours Use as preparation of choice procaine penicillin G in oil with 2% aluminum monostearate

2 Step up sulfonamide levels by administration of 0 5 gm each of sulfadiazine and sulfamerazine at 3 or 4 hour intervals

3 Double oral doses of aureomycin or chloramphenicol or increase intramuscular injections of streptomycin to 0 5 gm every four hours

4 With pulmonary involvement give aerosolization with 100 000 units of penicillin G and 0 5 gm of streptomycin per cc of physiologic saline

Continuing Care (Progressively Unfavorable Course)

1 Set up an intravenous drip Give alternately 1 million units of crystal line penicillin G in 30 cc of saline solution 2 5 gm each of *sodium sulfadiazine and sodium sulfamerazine in 200 cc* of molar lactate solution 500 mg of aureomycin hydrochloride in 200 cc of physiologic saline solution 50 mg of benadryl in 5 cc of 1% solution and 500 cc of whole citrated blood or 2 units of plasma

2 Repeat cycle of antibiotic antihistamine and supportive therapy with blood or plasma Omit sulfonamide if toxic symptoms arise persist with penicillin and streptomycin until the patient recovers or succumbs

3 All else failing resort to arsenotherapy injecting intravenously by syringe or in drip 60 mg arsenoxide (mapharsen)

ANTIBIOTICS

Innumerable antibiotic substances exist in nature Illustrative of the rapid strides in antibiotic therapy is the fact that of the twenty three preparations listed in 1946 (Table 13 p 103) only four appear in the roster which follows immediately Already obsolete are actinomycetin actinomycin A actinomycin B allicin canavalin chlorellin citrinin clavacin patulin claviformin clavatin flavicin flavacidin fumigacin helvolic acid fumigatin gigantic acid gliatoxin gramicidin lysozyme penicillic acid pyocyanase and pyocyanine

Antibiotics in common usage are discussed under separate entries

ANTICOAGULANT DRUGS

The pharmacology therapeutics and toxic manifestations produced by the anticoagulant drugs heparin and Dicumarol have been pre viously discussed (pp 1050–1052) We still adhere to the opinion that

ANTIBIOTICS OF BIOLOGIC ORIGIN

Preparation	Origin	Bacterial Spectrum
Aerosporin	B polymyxa	Gram negative bacilli Not commercially available
Aureomycin	Streptomyces aureofaciens	Includes cocci bacilli rickettsia treponemes and viruses Commercially available Council accepted
Bacillomycin	B subtilis	Fungi. Not commercially available
Bacitracin	B subtilis	Topical use against cocci bacilli treponemes and amebas Commercially available for local use
Chloramphenicol (Chloromycetin)	Streptomyces venezuelae	Parallels aureomycin Commercially available Council accepted
Circulin	B circulans	Cocci bacilli and fungi. Not commercially available
Dihydrostreptomycin	From streptomycin	As streptomycin but less toxic Commercially available Council accepted
Garlicin	Garlic	*Especially gram negative bacilli* Not commercially available
LL 47	Aspergillus	Experimental use against virus influenza
Litmocidin	Pro-actinomyces	Experimental (M tuberculosis V comma)
Lupulin	Hops	Experimental (M tuberculosis)
Neomycin	Streptomyces	As streptomycin but less toxic and fewer resistant bacterial forms Not commercially available
Pectin	Apple	Influenza virus
Penicillin	Penicillium notatum	Includes gram negative and positive cocci gram positive bacilli and treponemes Commercially available and Council accepted.
Polymyxin	B polymyxa	Especially gram negative bacilli Not commercially available
Streptomycin	Streptomyces griseus	Cocci and bacilli especially gram negative and M tuberculosis Commercially available Council accepted
Subtenolin	B subtilis	Active against M tuberculosis Not commercially available
Terramycin	Streptomyces rimosus	As aureomycin Commercially available
Tyrothricin	B dubos	Topical use again t bacilli mostly gram positive Commercially available Council accepted

heparin is best adapted for use by the general practitioner whereas Dicumarol the specialist preparation of choice is too treacherous for use outside of fully equipped establishments

Dicumarol versus Heparin

Dicumarol produces hypo prothrombinemia (p 1109) Effective doses productive of prothrombin levels between 20 and 30% of normal pre

vent intravascular clotting without causing hemorrhagic manifestations Dicumarol is effective when given orally Drug costs with Dicumarol anticoagulant therapy are minimum

However the lesser cost of Dicumarol is nullified by the increased cost of necessary laboratory procedures Its ease of administration is canceled by the uncertainty of its effect the unreliability of prothrombin determinations even in the hands of experts and the serious hazards of toxicity notably bleeding

Heparin is an effective anticoagulant through its triple threat activity as antithromboplastin antiprothrombin and antithrombin So far as is known it does not function through damage to liver cells

The anticoagulant effect is apparent in a very few minutes Given by subfascial deposit the anticoagulant effect of adequate doses persists for twenty four to seventy two hours Hyperheparinemia is instantly controlled by intravenous injection of protamine which is antidotal in the proportion of mg for mg Thus intravenous introduction of 10 cc of *2% protamine offsets the anticoagulant effect of 200 mg of heparin*

In contrast to Dicumarol bleedings significant hemorrhage associated with hyper heparinemia must be exceedingly rare Loewe the originator of the depot method in an extensive experience has never had occasion to use protamine for its antidotal effects

Heparin activity may be gauged with reasonable accuracy by estimation of the coagulation time (Lee White Howell) measurable at the bedside (p 4572) The practitioner may decide immediately on determination of the results whether or not to give a deposit and approximately what dose is required

The overall cost of heparin admittedly great is less than the overall cost of Dicumarol to which must be added laboratory fees for prothrombin estimations

Available Preparations

Dicumarol N N R Tablets 25 50 and 100 mg (Abbott Merrell Schieffelin) For initial loading dose give 200 to 300 mg orally for average maintenance dose 100 to 200 mg daily depending on estimates of prothrombin time

Tromexan (4 4 dihydroxy dicumarnyl ethyl acetate) a commercial preparation not yet widely distributed For parenteral Dicumarol therapy requires injections at approximately 12 hour intervals as indicated by prothrombin tests

Heparin Solution N N R (10 cc vials made so that 1 cc = 10 mg (Abbott Upjohn) For continuous intravenous drip injection add 15 cc to 1000 cc of saline diluent For intermittent intravenous injection introduce by syringe method The unofficial Liquaemin (Roche) is identical in composition and strength with the official preparation

Depo Heparin Sodium (Upjohn) 1 cc cartridges with disposable syringe Contain 200 mg of heparin in gelatin and dextrose with and without vasoconstrictors (epinephrine 1 mg and ephedrine 10 mg)

Heparin Pitkin (Warner) ampuls 2 cc = 200 mg 3 cc = 300 mg In gelatin and dextrose with and without vasoconstrictors

Practical Therapeutics

Dicumarol

1 If Dicumarol is used for anticoagulant action follow directions issued by the American Heart A sociation which require that pro thrombin determinations be made daily and which forbid an order of Dicumarol until the morning prothrombin report is available

2 Order 200 to 300 mg of Dicumarol daily until prothrombin time by the Link Shapiro method is reported at thirty seconds

3 Give fifty to 100 mg of Dicumarol daily if prothrombin time is between thirty and thirty five seconds

4 When prothrombin time again reaches thirty seconds or less give drug cautiously in 100 mg doses

5 Continue Dicumarol for a minimum period of thirty days following the last thrombotic or thromboembolic episode

6 In the presence of hemorrhage due to drug inject sixty to seventy five mg of synthetic vitamin K (menadione) intravenously and obtain *fresh whole blood or plasma for intravenous introduction*

Heparin

1 Before depositing heparin subfascially obtain coagulation time (p 4572) estimate blood pressure gradient and note the patient s approximate weight

2 If the patient weighs in excess of 150 lbs administer 300 to 400 mg of anticoagulant Give the larger dose to obese thrombophils use smaller dose for lighter patients with more nearly normal coagu lation times

3 Unless there is some contra indication (such as hypertension) prefer heparin with vasoconstrictor This preparation is particularly uitable in acute coronary occlusion associated with shock and in pulmonary embolizations complicated by forward failure

4 If addition of vasoconstrictor to anticoagulant causes increase in local reaction or sympathomimetic manifestations (tachycardia eleva tion of blood pressure sweating pallor anxiety precordial distress etc) substitute the product without vasoconstrictor The latter produc ing elevation of coagulation time over therapeutic levels for only twenty four hours requires more frequent introduction Addition of vasoconstrictor probably doubles the effective period of the anti coagulant

5 To patients weighing less than 150 lbs give 200 to 300 mg for the initial deposit Use larger amount for thrombophiles and lesser amount for lighter patients with more nearly normal coagulation times

6 Caution the patient that a local reaction may be experienced within four to six hours and that discomfort may last for two to twenty four hours Leave an order for subcutaneous injection of 100 mg of demerol or of 5 mg of dolophine repeated at hourly intervals at least thrice if necessary Advise the patient to request relief as soon as dis comfort is noted

7 Forbid local applications of ice or heat to the inflamed area The former delays and the latter accelerates liberation of anticoagulant from the deposit

8 For convenience favor depo heparin (Upjohn) The product is packaged in a disposable syringe greatly facilitating introduction by the practitioner it is marketed in doses of 200 mg with and without vasoconstrictor and local reactions appear to be less severe and less frequently encountered than with other preparations If there is hesitancy about use of vasoconstrictor one deposit can be made with pure anticoagulant and the other with the combination of anticoagulant and adrenergen

9 Once daily during anticoagulant therapy with heparin obtain coagulation time by the bedside method Try to keep the coagulation time between twenty five and forty seconds Readings in excess of forty seconds suggest an approach to hyperheparinization which requires no therapy so long as the patient has no hemorrhagic manifestations Readings below twenty seconds indicate insufficient dosage particularly if drawn blood fails to layer leaving a clear supernatant fluid

10 If coagulation time is in excess of forty five seconds omit heparin therapy for that day

11 If coagulation time is between twenty and forty five seconds omit heparin therapy for that day

12 If coagulation time is below twenty seconds but the phenomenon of layering is observed inject 200 mg preferably with vasoconstrictor

13 If coagulation time is less than twenty seconds and blood clots deposit 300 mg

14 Continue heparin deposits for at least three weeks after last thrombotic or embolic episode

15 *In the presence of a prolonged coagulation time and hemorrhagic* manifestations that are obviously due to hyper heparinemias prepare to inject intravenously 2 cc of protamine Figure that protamine neutralizes heparin mg for mg Give 5 cc of 2 per cent solution for each 100 mg of estimated overdosage Repeat at 2 hour intervals or sooner if necessary

ANTIGENS

Numerous antigens have been prepared from the bodies or toxic products of invading microbes In clinical medicine these are used for induction of artificial active immunity (p 75) Antigens have extraordinary value in preventive medicine Their universal use could eliminate cholera diphtheria whooping cough plague smallpox tetanus typhoid fever tularemia typhus fever and yellow fever

Induction of artificial active immunity is encouraged early in life Most pediatrists favor an *immunization schedule* (p 4363) beginning at six months to protect against *diphtheria tetanus whooping cough* and smallpox Later typhoid immunizations are added Inoculations

against plague cholera typhus and yellow fevers are instituted when there is need

Attention is drawn in this place to perversions of artificial active immunity that result in hypersensitivity phenomena (p 4163) Although histamine type and tuberculin type hypersensitivities are rarely caused by microbic antigens an occasional encephalopathy following small pox or rabies vaccination serves as a reminder that even these great boons to preventive medicine have their price

Antigens used for therapy in medical practice may be rated as follows

Proven Prophylactic Value Cholera diphtheria pertussis plague rabies Rocky Mountain spotted fever smallpox tetanus typhoid typhus yellow fever

Investigational Consideration Actinomycin BCG blastomycin coccidioidin epidemic encephalitis equine encephalitis histoplasmin influenza AB virus measles poliomyelitis and St Louis encephalitis

Useless Acne arthritis catarrhalis cold entoral Friedlander furunculosis gonococcus orovax B influenza respiratory rheumatic fever rheumatoid arthritis staphylococcal streptococcal and ulcerative colitis

Obsolete Brucellosis Ducrey bacillary dysentery erysipelas meningococcus paratyphoid pneumococcus scarlet fever toxin and tularemia

ANTIGENS USED IN DIAGNOSIS AND THERAPY

Acne Vaccine
(Cutter Kirk Lilly Parke Davis Pitman Moore Sharp & Dohme Sherman)
Prepared from corynebacterium acnes staphylococci and E coli Not recommended

Actinomycosis Vaccine
For desensitization (p 4141) Not commercially available Obtain from National Institute of Health, Bethesda Maryland

Arthritis Vaccines
(Cutter Lederle Lilly National Parke Davis Pitman Moore Sherman)
Usually contain staphylococci streptococci pneumococci H influenzae M catarrhalis Kl pneumoniae (Friedlander) etc Not recommended

BCG (Bacillus Calmette Guerin)
An attenuated strain of M tuberculosis presently used experimentally for purposes of immunization (p 4602) Not yet commercially available

Blastomycin
For vaccine treatment of blastomycosis (p 4255) Not commercially available but may be obtained from Dr Donald F Martin Duke University School of Medicine Durham N C

Brucella Vaccine N N R
(Lederle National Pitman Moore)
Prepared from Br melitensis suis and abortus Of dubious prophylactic value Replaced for therapy by aureomycin (p 4271)

Catarrhalis Vaccine
(Abbott Kirk Lederle Lilly National Parke Davis Pitman Moore Sharp & Dohme Sherman, Squibb)
Mixtures of M catarrhalis Kl pneumoniae pneumococci streptococci staphylococci etc Not recommended

Cholera Vaccine U S P
(Lilly)
Valuable prophylactic agent (p 4284)

Coccidioidin
Unofficial preparation not commercially available Obtain from Dr John Kessel

7 Forbid local applications of ice or heat to the inflamed area The former delays and the latter accelerates liberation of anticoagulant from the deposit

8 For convenience favor depo heparin (Upjohn) The product is packaged in a disposable syringe greatly facilitating introduction by the practitioner it is marketed in doses of 200 mg with and without vasoconstrictor and local reactions appear to be less severe and less frequently encountered than with other preparations If there is hesi tancy about use of vasoconstrictor one deposit can be made with pure anticoagulant and the other with the combination of anticoagulant and adrenergen

9 Once daily during anticoagulant therapy with heparin obtain *coagulation time by the bedside method Try to keep the coagulation* time between twenty five and forty seconds Readings in excess of forty seconds suggest an approach to hyperheparinization which requires no therapy so long as the patient has no hemorrhagic manifestations Readings below twenty seconds indicate insufficient dosage particu larly if drawn blood fails to layer leaving a clear supernatant fluid

10 If coagulation time is in excess of forty five seconds omit heparin therapy for that day

11 If coagulation time is between twenty and forty five seconds omit heparin therapy for that day

12 If coagulation time is below twenty seconds but the phenomenon of layering is observed inject 200 mg preferably with vasoconstrictor

13 If coagulation time is less than twenty seconds and blood clots deposit 300 mg

14 Continue heparin deposits for at least three weeks *after last* thrombotic or embolic episode

15 In the presence of a prolonged coagulation time and hemorrhagic manifestations that are obviously due to hyper heparinemias prepare to inject intravenously 2 cc of protamine Figure that protamine neutral izes heparin mg for mg Give 5 cc of 2 per cent solution for each 100 mg of estimated overdosage Repeat at 2 hour intervals or sooner if necessary

ANTIGENS

Numerous antigens have been prepared from the bodies or toxic products of invading microbes *In clinical medicine these are used for* induction of artificial active immunity (p 75) Antigens have extraor dinary value in preventive medicine Their universal use could elimi nate cholera diphtheria whooping cough plague smallpox tetanus typhoid fever tularemia typhus fever and yellow fever

Induction of artificial active immunity is encouraged early in life Most pediatrists favor an *immunization schedule* (p 4363) beginning at six months to protect against diphtheria tetanus whooping cough and smallpox Later typhoid immunizations are added Inoculations

ANTIGENS USED IN DIAGNOSIS AND THERAPY—Continued

Frei Antigen
(Lederle)
For test use in lymphogranuloma venereum (Fig 72 D p 470)
Friedlander Vaccine
(Sherman)
Contains Kl pneumoniae pneumococci streptococci M catarrhalis and staphylococci Not recommended.
Furunculosis Vaccine
(Kirk Lilly National Drug Parke Davis Pitman Moore Sherman)
Suspension of killed staphylococci Not recommended. Prefer prophylactic use of antibiotics (p 4362)
Gonococcus Vaccine
(Kirk Lilly Parke Davis Pitman Moore Sherman)
Prefer antibiotic prophylaxis with sulfonamide or preferably penicillin.
Histoplasmin
For skin te t in histoplasmo.i Not commerciall/ available
Influenza Vaccine (Bacterial)
(Kirk Lilly Parke Davis Pitman Moore Sharp & Dohme Sherman Upjohn)
Suspension of killed H influenzae combined with pneumococci streptococci and other respiratory organisms Not recommended. Do not confuse with influenza virus vaccine Types A and B
Influenza Virus Vaccine Types A and B N.N.R
(Lilly Pitman Moore Sharp & Dohme Squibb)
Formaldehyde killed suspension of influenza virus consisting of 50% type A virus and 50% type B virus grown in extra-embryonic fluids of developing chick. For use in active immunity against viral influenzal infections especially when epidemic threatens (p 4372) Employ cautiously in allergic patients Precede by skin test for sensitivity
Lygranum S T
(Squibb)
Lymphogranuloma venereum antigen of chick embryo origin for Frei test (Fig 72 D p 470) Do not confuse with Lygranum C F used in complement fixation test.
Measles Vaccine
Experimental use only (p 4400)
Meningococcus Vaccine
(Sherman)
Prefer antibiotic prophylaxis with sulfonamide or penicillin (p 4362)
Oravax
(Merrell)
For oral use Not recommended
Paratyphoid Vaccine
Not recommended Use typhoid vaccine alone
Pertussis Vaccine N N.R
(Cutter Kirk, Lederle Lilly National Drug Parke Davis Pitman Moore Sharp & Dohme Sherman Squibb Upjohn Wyeth)
Use pertussis vaccine for booster doses (p 4463) For routine use prefer triple immunization with diphtheria toxoid, alum precipitated, tetanus toxoid alum precipitated, and pertus is vaccine
Pertussis Vaccine Alum Precipitated N N.R
(National Drug Parke Davis Upjohn)
May be preferable to plain suspensions above
Pertussis Vaccine Combined with Diphtheria Toxoid
See diphtheria toxoid above
Pertussis Vaccine Combined with Diphtheria and Tetanus Toxoids
See diphtheria toxoid above
Plague Vaccine U S P
(Cutter)
Highly efficacious for prophylaxis (p 4467)

ANTIGENS USED IN DIAGNOSIS AND THERAPY—Continued

Los Angeles General Hospital Los Angeles (33) California U e for skin test ing and treatment of coccidioidomycosis (p 4289)

Cold Vaccine
Oral catarrhalis and respiratory vaccines Not recommended

Coli Vaccine
(Lilly Pitman Moore)
To combat urinary infections Not recommended

Diphtheria Toxin Diagnostic U S P
(Cutter Lederle Lilly National Drug Parke Davis Pitman Moore Sharp & Dohme Squibb Wyeth)
For Schick test (Fig 43 p 302) Not u ed therapeutically

Diphtheria Toxin Antitoxin Mixture N N R.
Obsolete Prefer Toxoid alum precipitated

Diphtheria Toxoid U S P
(Cutter Lederle Lilly National Drug Parke Davis Sharp & Dohme Squibb Wyeth)
Prefer diphtheria toxoid alum precipitated U S P

Diphtheria Toxoid Alum Precipitated U S P
(Lederle Lilly National Drug Parke Davis Pitman Moore Sharp & Dohme Squibb Wyeth)
Use for booster dose primarily For routine immunization, schedule prefer diphtheria toxoid, alum precipitated, tetanus toxoid, alum precipitated, per tu sis vaccine combined (p 4365)

Diphtheria Toxoid Tetanus Toxoid Alum Precipitated U S P
(Lederle Lilly National Drug Parke Davis Pitman Moore Sharp & Dohme Squibb Wyeth)
Prefer combination with pertussis vaccine for routine use

Diphtheria Toxoid Alum Precipitated Tetanus Toxoid Alum Precipitated and Per tussis Vaccine Combined N.N R
(National Drug Sharp & Dohme Squibb)
For simultaneous immunization against whooping cough diphtheria and teta nus Recommended for routine use especially in infancy See immunization schedule (p 4365)

Diphtheria Toxoid Combined with Pertussis Vaccine U S P
(National Drug Parke Davis Sharp & Dohme Upjohn)
Prefer combination with tetanus toxoid

Ducrey Vaccine
(Lederle)
For use in Ito Reenstierna skin test for chancroid (Fig 41 p 289)

Dysentery Vaccine
(Parke Davis)
Polyvalent suspension of shigellae For prophylaxis prefer antibiotic effects of sulfonamide and aureomycin (p 4362)

Encephalitis Vaccine (Herpes F Strain)
(Lederle)
A 10% rabbit brain suspension of virulent neurotropic herpes virus inacti vated by formaldehyde For use in acute and chronic stages of epidemic and other forms of encephalitis Unofficial but worthy of trial for lack of more effec tive specific therapy

Entoral
(Lilly)
Contains pneumococci streptococci M catarrhalis and H influenzae Not recommended

Equine Encephalomyelitis Vaccine
(Lederle)
Formalinized chick embryo culture of eastern and western strains of virus For human use to stimulate production of protective antibodies Give 1 cc subcutaneously Repeat after one week (p 4309)

Erysipelas Vaccine
(Sherman)
Prefer antibiotic prophylaxis with sulfonamide or penicillin (p 4447)

ANTIGENS USED IN DIAGNOSIS AND THERAPY—Continued

Staphylococcus Immunogen
(Parke Davis)
Not recommended. Prefer antibiotic prophylaxis and treatment with sulfonamide and/or penicillin.

Staphylococcus-Streptococcus Vaccine Combined N.N.R.
Not recommended. Prefer antibiotic prophylaxis and treatment with sulfonamide and/or penicillin.

St. Louis Encephalitis Vaccine
Not commercially available. For experimental use only in an epidemic (p. 4310). Consult U.S. Public Health Service

Tetanus Toxoid U.S.P.
(Lederle)
Prefer tetanus toxoid, alum precipitated.

Tetanus Toxoid Alum Precipitated U.S.P.
(Lederle Lilly National Drug Parke Davis Pitman Moore Sharp & Dohme Squibb Wyeth)
Use tetanus toxoid for "booster" dose annually or when indicated. For routine use prefer diphtheria toxoid, alum precipitated, tetanus toxoid, alum precipitated, pertussis vaccine combined.

Trichinella Extract
(Lederle Lilly)
For diagnostic aid only in intradermal skin test for trichinosis (Fig. 91, p. 541)

Trichophyton
(Lilly)
For diagnostic use only in determining sensitization to trichophytoses (p. 4334)

Tuberculin Old (O.T.)
(Lederle Lilly Parke Davis)
For von Pirquet cutaneous test (Fig. 34, p. 263). Use contents of capillary tubes. For Mantoux test, start with vial in which 1 cc contains 0.001 cc of Old Tuberculin.

Tuberculin Patch Test
(Lederle)
For testing of skin sensitivity by the method of Volmer (Fig. 35, p. 264)

Tuberculin Purified Protein Derivative (P.P.D.)
(Parke Davis, Sharp & Dohme)
For injection into the skin of subjects to test for tuberculin sensitivity

P Tularensis Vaccine
Obsolescent through efficacy of aureomycin.

Typhoid Vaccine U.S.P.
(Cutter Lilly National Drug Park Davis Pitman Moore Standard)
For routine immunization against typhoid fever. Mandatory under all conditions. Give "booster" doses every 3 to 5 years or when needed. Prefer straight typhoid vaccine to mixture with paratyphoid organisms. Latter produces local and systemic reactions but very little significant or lasting immunity.

Typhus Vaccine
(Parke Davis)
Of definitive value for the production of active immunity in the prevention of epidemic typhus. Give 1 cc injections subcutaneously at 7- to 10-day intervals, for three doses.

Ulcerative Colitis Streptococcus Vaccine
(Kirk, Parke Davis Sherman)
Unofficial preparation. Not recommended.

Undulant Fever Vaccine
See Brucella Vaccine

Whooping Cough Vaccine
See Pertussis Vaccine

Yellow Fever Vaccine
Virus vaccine. Not commercially available but exceedingly effective. Obtain from U.S. Public Health Service. Now irradiated to prevent virus hepatitis

ANTIGENS USED IN DIAGNOSIS AND THERAPY—Continued

Pneumococcus Antigen
(Lilly)
Suspension of partially autolyzed pneumococci Unofficial and not recommended Prefer antibiotic prophylaxis with sulfonamide or penicillin

Pneumococcus Polysaccharides (Type Specific)
(Squibb)
Antigenic solutions of purified capsular polysaccharides of commoner types of pneumococci Unofficial and not recommended. Prefer antibiotic prophylaxis with sulfonamide or penicillin (p 4362)

Pneumonia Vaccine Combined
(Parke Davis)
Contains pneumococci Kl pneumoniae streptococci etc Unofficial and not recommended Prefer antibiotic prophylaxis with sulfonamide or penicillin

Poliomyelitis Vaccine
Experimental

Rabies Vaccine U S P
(Harris Lilly Cutter Lederle National Drug Sharp & Dohme Squibb Standard Wyeth Pitman Moore)
Pecommended only where there is definitive need (p 4487) May cause encephalitis due to tuberculin type hypersensitivity reaction (p 4307) Consider carefully

Respiratory Vaccines
(Lilly National Drug etc)
Not recommended

Rheumatic Arthritis Vaccine
(Lederle)
Unofficial preparation Not recommended

Rheumatic Fever Vaccine
(Parke Davis)
Unofficial preparation Not recommended

Rocky Mountain Spotted Fever Vaccine
(Lederle)
Prepared by inoculating chick embryos with R rickettsii For prophylaxis use three injections subcutaneou ly of 1 cc at weekly intervals Give 1 cc booster annually to exposed

Scarlet Fever Streptococcus Toxin U S P
(National Parke Davis Sharp & Dohme Squibb Standard)
For diagnostic Dick test Not used for therapeutics

Scarlet Fever Streptococcus Toxin Tannic Acid Precipitated N N R
(Wyeth)
For active immunization in scarlet fever Not recommended Prefer antibiotic prophylaxis with penicillin

Scarlet Fever Streptococcus Antitoxin for Schultz Charlton Test
(National Drug)
For diagnosis only to produce blanching of specific eruption (Fig 18 p 164)

Smallpox Vaccine U S P
(Cutter Lederle Lilly National Drug Parke Davis Sharp & Dohme Squibb Wyeth)
For vaccination against smallpox Routine use advised after the age of six months Repeat every three to five years

Staphylococcus Vaccine
(Kirk, Lilly Parke Davis Pitman Moore Sherman Wyeth)
Not recommended Prefer antibiotic prophylaxis with sulfonamide or penicillin

Staphylococcus Toxoid N N R
(Lederle National Drug Parke Davis Pitman Moore Sharp & Dohme)
Not recommended Prefer antibiotic prophylaxis and treatment with sulfonamide or penicillin.

Staphylococcus Bacteriophage
(Parke Davis)
Not recommended Prefer antibiotic prophylaxis and treatment with sulfonamide and/or penicillin

ANTIGENS USED IN DIAGNOSIS AND THERAPY—Continued

Staphylococcus Immunogen
(Parke Davis)
Not recommended. Prefer antibiotic prophylaxis and treatment with sulfonamide and/or penicillin.

Staphylococcus Streptococcus Vaccine Combined N N R
Not recommended. Prefer antibiotic prophylaxis and treatment with sulfonamide and/or penicillin.

St Louis Encephalitis Vaccine
Not commercially available For experimental use only in an epidemic (p 4310) Consult U.S Public Health Service

Tetanus Toxoid U S P
(Lederle)
Prefer tetanus toxoid, alum precipitated.

Tetanus Toxoid Alum Precipitated U S P
(Lederle Lilly National Drug Parke Davis Pitman Moore Sharp & Dohme Squibb Wyeth)
Use tetanus toxoid for 'booster dose annually or when indicated For routine use prefer diphtheria toxoid, alum precipitated tetanus toxoid, alum precipitated, pertussis vaccine combined

Trichinella Extract
(Lederle Lilly)
For diagnostic aid only in intradermal skin test for trichino is (Fig 91 p 541)

Trichophyton
(Lilly)
For diagnostic use only in determining sensitization to trichophytoses (p 4334)

Tuberculin Old (O T)
(Lederle Lilly Parke Davis)
For von Pirquet cutaneous test (Fig 34 p 263) Use contents of capillary tubes For Mantoux test start with vial in which 1 cc contains 0 001 cc of Old Tuberculin.

Tuberculin Patch Test
(Lederle)
For testing of skin sensitivity by the method of Vollmer (Fig 35 p 264)

Tuberculin Purified Protein Derivative (P P D)
(Parke Davis Sharp & Dohme)
For injection into the skin of subjects to test for tuberculin sensitivity

P Tularensis Vaccine
Obsolescent through efficacy of aureomycin

Typhoid Vaccine U S P
(Cutter Lilly National Drug Park Davis Pitman Moore Standard)
For routine immunization against typhoid fever Mandatory under all conditions Give booster doses every 3 to 5 years or when needed Prefer straight typhoid vaccine to mixture with paratyphoid organisms Latter produces local and systemic reactions but very little significant or lasting immunity

Typhus Vaccine
(Parke Davis)
Of definitive value for the production of active immunity in the prevention of epidemic typhus Give 1 cc injections subcutaneously at 7 to 10 day intervals for three doses

Ulcerative Colitis Streptococcus Vaccine
(Kirk Parke Davis Sherman)
Unofficial preparation Not recommended

Undulant Fever Vaccine
See Brucella Vaccine

Whooping Cough Vaccine
See Pertussis Vaccine

Yellow Fever Vaccine
Virus vaccine Not commercially available but exceedingly effective Obtain from U S Public Health Service Now irradiated to prevent virus hepatitis

ANTIHISTAMINES

The present roster of therapeutic products for use in the treatment of acute histamine type allergic hypersensitivities (p 4166) lists past failures and evaluates the current status of histamines histaminases and histamine antagonists

Past Failures

The risks and difficulties of specific desensitization in Allergy encouraged early experimenters to seek non specific methods Up to 1932 at least 165 trials were made with barium sulfate barium chloride atropine ether chloral hydrate nonspecific serums and proteins de ensitization with heterologous antigen benzene heparin inter current infection with M tuberculosis and reduction in barometric pressure

Between 1932 and 1936 many additional measures aimed at non specific inhibition of anaphylactic shock and allergic manifestations were propo ed These included prescriptions of barbital pernoston tribromoethanol potassium salts sodium thiosulfate ascorbic acid (vitamin C) hesperidin (vitamin P) and ethylene disulfonate (allergosil) Each of the e products was found useless or of doubtful value Despite enthusiastic claims Allergosil particularly was reported ineffectual by the Committee on Medicaments and Pharmaceuticals of the American Academy of Allergy (Dec 9 1945)

Histamine

Desensitization therapy with histamine was given impetus by Horton who described the syndrome of erythromelalgia of the head characterized by periodic attacks of migraine associated with ipselateral rhinorrhea lacrimation and engorgement of temporal vessels These manifestations reproduced by injections of 0 3 to 0 5 mg of histamine and relieved by desensitization with subcutaneous injections of increasing doses of histamine were interpreted as consequences of histamine release

Method of Treatment For desensitization therapy of erythromelalgia of the head commercially available solutions of histamine diphosphate are employed The weaker solution which contains 0 275 mg of histamine diphosphate is the equivalent of 0 1 mg of histamine base the stronger solution contains 2 75 mg of the diphosphate and 1 mg of the base per cc

Unusually sensitive patients are started with 1 10 solution of the weaker preparation in order to avoid histamine shock with flushing tachycardia vertigo fall of blood pressure nausea and abdominal cramps Histamine shock may be alleviated by subcutaneous injection of 0 5 to 1 cc of epinephrine hydrochloride (1 1 000) which should be held available in case of need

At first it is recommended that daily injections of sensitizing solution be given Later intervals may be increased to two days or a week Starting with 1 10 dilution of the weaker solution (containing 0 1 mg of histamine base per cc) an initial injection of 0 1 cc is made subcutaneously depending then on patient response the dose of 1 10 solution is increased until undiluted weaker solution is tolerated in the minimum dose of 0 1 cc When the full 1 cc do e of weaker solution can be injected without significant toxicity the patient is promoted to stronger solution containing 2 75 mg of histamine diphosphate or 1 mg

of histamine base per cc The maximum do^e consi.ts of the contents of a full ampul (1 cc) This full therapeutic dose may be given at weekly intervals for a considerable period depending entirely on the patient response

Though many authors confirm the views and findings of Horton our experiences coincide with those of Feinberg (J A M A 132 702 1946) who states that injections of histamine in man do not increase tolerance the effectiveness of histamine in allergic conditions has been exaggerated whatever beneficial results are obtained must be explained on a basis other than desensitization to histamine

Histamine-Azoprotein (Hapamine)

Efforts to desensitize patients with a preparation of histamine azoprotein (hapamine) appear to be as unsatisfactory as those employing unbound histamine The Committee on Pharmaceuticals and Medicaments of the American Academy of Allergy (1945) reported that those who have given histamine azoprotein a fair trial found it either totally ineffective or have been able to attribute whatever measures of effectiveness it has to its non specific action

Histaminase (Torantil)

With the discovery that some tissues contain a substance or enzyme capable of destroying histamine a commercial preparation of hista mina e (torantil) wa. developed Once again impartial investigators concluded that the results of histamina e therapy were unimpressive and that histaminase lacks a specific effect in allergic conditions

Histamine Antagonists (Antihistamines)

In contrast to disappointments encountered with bound and un bound histamine and histaminases newly developed antihistamines or histamine antagoni.ts have proven remarkably effective in palliating clinical manifestations resulting from histamine type hypersensitivities (p 4166)

Of the many preparation. commercially available the Council on Pharmacy of the American Medical Association granted first recogni tion to diphenhydramine hydrochloride (benadryl) and tripelennamine hydrochloride (pyribenzamine) and later to neohetramine and thenylene Other preparations as yet not officially accepted (1950) have actions similar to benadryl and pyribenzamine They afford the practitioner broad latitude when Council accepted products fail in their action or when patients exhibit idiosyncrasy or untoward response to official preparation. (see Table p 4212)

Pharmacology

Antihistamines do not influence the fundamentally deranged mechan isms productive of hypersensitivity (p 4163) They merely neutralize the effect of the offending chemical In this respect their palliative action is comparable to that of opiate in the relief of pain

COMMERCIALLY AVAILABLE HISTAMINES HISTAMINASES AND ANTIHISTAMINES (HISTAMINE ANTAGONISTS)

Trade Name and Manufacturer	Chemical Name	Available Preparations and Doses	Notes
ALLERGOSIL	Ethylene Disulfonate		Ineffective preparation.
ANTHALLAN (Medico)	3-di(n butyl)amino-methyl-4 5 6-trihydroxybenzo-1 2) furan 1 (3)-one	Capsules 65 mg Average 6 daily	Not recommended. Relatively ineffectual Hypersensitivity and idiosyncrasy noted.
ANTISTINE (Ciba)	Phenazoline hydrochloride	Tablets 100 mg Ophthalmic solution 0 5% Nasal solution, 0 5% isotonic buffered.	Ophthalmic and nasal solutions particularly effective Use 1 to 3 drops every few hours as needed. Tablets low potency and may produce wakefulness
BENADRYL (Parke Davis) N N R.	Diphenhydramine hydrochloric acid	Kapseals 25 mg 50 mg Elixir (0 25%) 4 cc = 50 mg Injectable (1%) 5 cc = 50 mg Cream (2%) Emplets (delayed action) 50 mg Kapseals 50 mg with 10 mg ephedrine	Kapseals and Elixir efficacious and Council approved but cause considerable drowsiness Injectable solution for intramuscular and intravenous uses. Employ cream as antipruritic
CHLOR TRIMETON MALEATE (Schering)	Chlorprophen pyridamine maleate	Tablets 4 mg	Smallest effective dose with minimum side effects and relatively high therapeutic efficacy
DECAPRYN (Merrell)	Doxylamine succinate	Tablets 25 mg	Effective and protracted action causing considerable drowsiness
DIATRIN HYDROCHLORIDE (Warner)	N N-dimethyl N phenyl N (2 thienyl methyl) ethylenediamine mono hydrochloric acid	Tablets (sugar coated) 50 mg	Effective and of low toxicity
DRAMAMINE (Searle)	Beta dimethylaminoethyl benzohydryl ether 8-chlorotheophyllinate	Tablets 100 mg	Seasickness specific
HAPAMINE (Parke Davis) Histamine Azoprotein	Histamine and despeciated hor e serum globulin for antihistamine immunization	Vial 5 cc Inject subcutaneously 0 01 cc and increase by 0 05 cc to maximum dose of 1 cc at intervals of four days if no reaction	Not recommended Prefer use of antihistamines orally

Trade Name and Manufacturer	Chemical Name	Available Preparations and Doses	Notes
HISTADYL (Lilly)	Thenyl pyramine hydrochloric acid	Pulvules, 25 mg., 50 mg 100 mg Enseals, 50 mg Syrup (5 cc. = 25 mg) Cream (2%) Pulvules histadyl 25 mg., ephedrine 8 mg Ampuls, 1 cc. = 20 mg Ophthalmic ointment 0 5%.	Effective with occasional drowsiness.
HISTAMINE PHOSPHATE or DIPHOSPHATE (Abbott, Lilly)	Beta iminazolethylamine	Ampuls 0 275 mg (0 1 mg histamine base) and 2 75 mg (1 mg histamine base)	As diagnostic aid in gastric acidity test (p 3722) As desensitization agent (p 4210)
HYDRYLLIN (Searle)	Diphenhydramine (25 mg) with aminophyllin (100 mg)	Tablets 25 mg Elixir (8 cc. = 1 tablet)	Effective especially in bronchospasm, due to synergism with aminophyllin.
NEO ANTERGAN MALEATE (Merck)	Pyranisamine maleate	Tablets 25 mg 50 mg	Highly effective Side effects relatively frequent.
NEOHETRAMINE N N.R. (Wyeth)	Thonzylamine hydrochloric acid	Tablets 25 mg 50 mg 100 mg Syrup 25 mg = 4 cc	Highly effective Only occasional side effects
NETHAPHYL (Merrell)	Nethamine hydrochloric acid and theophylline	Capsules	See *Hydryllin*
PERAZIL (Burroughs Wellcome)	4-Chlorobenzhydryl piperazine monohydrochloride	Tablets 50 mg	Side effects infrequent. Single 50 mg dose generally provides relief for 2 to 24 hours.
PHENERGAN	N-dimethylamino-2 propyl 1 phenothiazine		Rarely used.
PYRIBENZAMINE N.N.R. (Ciba)	Tripelennamine hydrochloric acid	Tablets 50 mg (delayed action) 50 mg 25 mg with 12 mg ephedrine Elixir (1 cc. = 5 mg) Ointment, 2% Cream, 2%. Nasal solution, 0 5%	Highly effective Council approved. Rare side effects
TAGATHEN (Lederle)	Chlorothen citrate	Tablets 25 mg Ointment, 2%.	Effective Rare side effects.

COMMERCIALLY AVAILABLE HISTAMINES HISTAMINASES AND ANTIHISTAMINES (HISTAMINE ANTAGONISTS) (*Continued*)

Trade Name and Manufacturer	Chemical Name	Available Preparations and Doses	Notes
THENYLENE hydrochloric acid N N R (Abbott)	Methapyrilene hydrochloric acid	Tablets 50 mg., 100 mg (sugar coated) Cream, 2%	Effective but with side effects.
THEPHORIN (Hoffmann LaRoche)	2 methyl 9 phenyl 2 3 4 9) tetrahydro-1 pyridindene hydrogen tartrate	Tablets 25 mg Syrup 1 cc = 2 5 mg Ointment, 5%	Effective Pare side effects
TORANTIL (Winthrop)	Histaminase	Tablets 10 units	Ineffectual preparation
TRIMETON (Schering)	Prophenpyramine	Tablets 25 mg Ointment, 3%	Effective Low toxicity

In addition to histamine antagonism many available preparations mildly depress the cerebrum reduce gastric secretion of hydrochloric acid and relax smooth muscle Hence they have some non specific therapeutic value as sedatives antacids and antispasmodics

Cerebral Depression Bed patients benefit by the combination of antihistaminic effect and sedation particularly when there are complaints of restlessness and itching

For the ambulatory patient however cerebral depression may be a serious untoward response Increased somnolence and disturbances of muscular co ordination may result in mental and manual inefficiency with increased accident hazard To offset these untoward reactions antihistamines are profitably combined with adrenergic cerebral stimulants in commercial preparations such as pyribenzamine ephedrine benadryl ephedrine and histadyl ephedrine

Gastric Antacid Reduction in gastric acidity and muscle tone is particularly useful in many patients who suffer as the result of hypertrophic gastritis Histamine antagonists may provide comfort to symptoms resulting from hyperacidity hypermotility and spasmosis

Smooth Muscle Depression Smooth muscle depression by the antihistamines is gainfully employed in the management of bronchospasm Synergism between histamine antagonist and aminophylline is provided by preparations which contain both ingredients such as hydryllin and nethaphyl

Toxicology

None of the histamine antagonists has important toxicology Most produce annoying side effects such as somnolence lethargy amnesia muscle incoordination numbness of lips and tongue dizziness and digestive symptoms such as anorexia nausea vomiting abdominal cramps or diarrhea Side effects usually are noted only after first administration of the preparation and disappear shortly thereafter If one

product causes persistent untoward manifestations another antihis tamine may be substituted

Comparison of the relative toxicities of benadryl and pyribenzamine (See Table p 4215) reveals that benadryl is much more likely to cause *drowsine..s vertigo numbne..s and asthenia whereas pyribenzamine* occasionally produces headache If a toxic response to either prepara tion is encountered the other should be substituted for limited trial Thereafter the selection may be an unofficial product such as trimeton chlorotrimeton diatrin tagathen or thephorin

Of untoward manifestations only amnesia and muscular incoordina tion are frequently encountered On a few occasions manifestations of blood dyscrasia have been reported but these are indeed rare and respond to di..continuance of medication

Choice of Preparation

The choice of histamine antagonist depends on the nature of clinical manifestations the proposed route of administration and the presence or absence of toxic side effects

BENADRYL vs PYRIBENZAMINE

Toxicity %

	Benadryl	*Pyribenzamine*
Drow iness	43	8 5
Nausea vomiting etc	8	9
Vertigo etc	7	3
Numbne s	6	1
Asthenia	4 5	2
Headache	0	2 5

Symptom Relief %

Acute urticaria	95	85
Chronic urticaria	87	79
Pruritus	20	61
Asthma (all types)	52	34
Vasomotor rhinitis (all types)	72	70
Dermatitis (all types)	66	57

Most experience with histamine antagonists has been with Council accepted benadryl and pyribenzamine It is suggested that the prac titioner begin *therapy with one or other of these tested preparations* unless there is some particular indication for initial use of one of the presently unofficial products (p 4212) Thus for example dramamine is specific in seasickness and hydryllin and nethaphyl (which also con tain aminophyllin) are seemingly more effective in the relief of bron chial asthma

The preference between benadryl and pyribenzamine so far as clinical manifestations are concerned is indicated above Pyribenza mine appears more effective as an antipruritic whereas benadryl is distinctly more valuable in the relief of asthma and the urticarias

Route of Administration

In part the choice of histamine antagonist depends on the proposed route of administration

ANTIHISTAMINES ROUTES OF ADMINISTRATION

Oral

Choose Council approved pyribenzamine or benadryl If ineffective or productive of side effects substitute neo-antergan diatrin, histadyl neohetramine tagathen thephorin trimeton etc (p 4212)

Oral (delayed)

For nocturnal symptoms especially use delayed action tablets of pyribenzamine or histadyl taken on retiring

Parenteral

Inject intramuscularly preferably but intravenously if necessary 1% benadryl (5 cc = 50 mg)

Ophthalmic Solution

Use collyrium of 0 5% antistine

Nasal Solution

Instill 0 5% antistine or 0 5% pyribenzamine (applied in nebulizer)

Skin Cream or Ointment

Apply 2% benadryl 2% pyribenzamine 2% tagathen, 2% histadyl or 5% thephorin

Therapeutics

Antihistamines are recommended for I specific prophylaxis of histamine type hypersensitivities (p 4166) II specific palliation of histamine type hypersensitivities (p 4167) III possibly specific prophylaxis in tuberculin type hypersensitivities (p 4169) and IV non specific *effects in a variety of unrelated conditions*

I *Specific Prophylaxis of Histamine type Hypersensitivities* Antihistamines are prescribed for prophylaxis (a) on exposure to highly *sensitizing non bacterial antigens* such as serum pollen cosmetics endocrine products sulfonamides etc (p 4179) (b) in infections by *highly sensitizing bacteria* (hemolytic streptococci tubercle bacilli etc)

SCHEDULE FOR ADMINISTERING PYRIBENZAMINE OR BENADRYL (mg)

Day	Breakfast	Lunch	Supper	Bedtime
1	50	50	50	0
2	50	50	50	50
3	50	50	50	100
4	50	50	100	100
5	50	100	100	100
6	100	100	100	100
7	100	100	100	150
8	100	100	150	150
9	100	150	150	150
10	150	150	150	150

As preventives oral administration of antihistamines is continued for at least two weeks after last known exposure to sensitizing agents

II *Specific Palliation of Histamine type Hypersensitivities* Histamine antagonists are used for active palliation of manifestations due to

histamine type hypersensitivity (p 4167) These include anaphylactic shock (p 549) serum sickness (p 548) seasonal vasomotor rhinitis (p 2098) bronchial asthma (p 2101) vernal conjunctivitis (p 1651) phlyctenular keratoconjunctivitis (p 1650) atopic dermatitis or infantile eczema (p 3342) contact dermatitis or dermatitis venenata (p 3330) dermatitis medicamentosa (p 3335) urticaria or hives (p 3345) angioneurotic edema (p 3349) disseminated neurodermatitis (p 3343) and idiopathic pruritus (p 1916)

For symptomatic treatment antihistamine is given as soon as hypersensitivities develop Variables in therapeutics are dependent on the nature of the symptoms the route of administration and the intensity of clinical manifestations For guidance the following suggestions are offered

1 Under ordinary circumstances oral administration suffices For first choice employ Council accepted pyribenzamine or benadryl

2 On the basis of lesser toxicity select pyribenzamine rather than benadryl except in urticarias and bronchospasm

3 For ordinary purposes total initial daily dose of either preparation is 200 mg The schedule (p 4216) of increasing quantities is followed until symptomatic relief is obtained provided that toxic side effects are not sooner encountered

4 With symptoms of great severity start the schedule with maximum amounts (as for tenth day in Chart p 4216) Decrease the total daily dosage as per schedule if the responses warrant

5 When symptomatic relief is obtained without untoward manifestations continue the optimum dose for several days Then gradually cut the dose provided that the patient remains comfortable

6 With persistent side effects from pyribenzamine and benadryl try products of minimum toxicity such as chlorotrimeton diatrin tagathen thephorin and trimeton

7 If speed of action is required inject 1% benadryl intramuscularly or intravenously For initial injection give 2 to 5 cc of 1% solution (20 to 50 mg) Repeat at hourly intervals provided that the patient does not get too drowsy Give slow intravenous injection if necessary after dilution with sufficient sterile saline to total 20 cc of solution

8 If injection of antihistamine alone does not suffice to control serious clinical manifestations (such as angioneurotic edema obstructing respiratory passages) take advantage of the synergism with adrenergen by use of combined oral product (histadyl with ephedrine) by simultaneous subcutaneous or intramuscular injection of 0 5 to 1 0 cc of epinephrine hydrochloride (1 1000) or by local spray of epinephrine hydrochloride 1 100

9 In bronchospasm add to antihistamine adrenergen synergism by simultaneous use of aminophyllin Latter may be exhibited in a combination product (hydryllin diatrin or nethaphyl) or separately by mouth or intravenously (0 5 gm)

10 Oral or parenteral antihistamine may be supplemented by local or topical applications using ointments of 2% benadryl 2% pyribenzamine 2% tagathen or 5% thephorin by collyrium of 0 5% antistine or by nasal instillations of 0 5% antistine or pyribenzamine

11 For patients who develop nocturnal symptoms (such as bronchospasm) prescribe pyribenzamine or histadyl in enteric coated products at bedtime

12 After recovery instruct the patient to resume antihistamine on *fresh exposure to offending allergen or if there is recurrence* of symptoms

III *Possibly Specific Prophylaxis of Tuberculin type Hypersensitivities* The action of antihistamine in tuberculin type hypersensitivities (p 4169) is not as obvious as in histamine type varieties The purpose of therapy is prevention of future damage rather than palliation of present symptomatology Because of the gravity of tuberculin type hypersensitivities (p 4174) any measure that gives promise for prophylaxis and holds no threat for increasing damage is highly recommended even though the rationale for therapy is admittedly hypothetical

Our *personal preferences for use of antihistamines in* tuberculin type hypersensitivities are summarized in the following axioms

1 Administer antihistamine routinely to every individual exposed to infection with highly sensitizing microorganisms such as the hemolytic streptococci or tubercle bacilli

2 Administer antihistamine routinely to the hypersensitive patient (p 4165) who is exposed to any infectious agent or to potentially sensitizing drug or biological (serum vaccine all biologicals antibiotics but especially sulfonamide and penicillin salicylate iodide phenolphthalein antithyroids dilantin etc)

IV *Non specific Indications* Non specific indications for use of antihistamines are so varied that they are best presented in chart form

NON SPECIFIC INDICATIONS FOR ANTIHISTAMINE THERAPY

Indication	Action
Gastric hyperacidity (p 1769)	Diminishes secretion of hydrochloric acid.
Gastro-intestinal spasmosis (p 1999)	Relaxes smooth muscle
Cerebral stimulation	Mild sedation and hypnosis
Chronic hypertrophic gastritis	Reduces secretion and relaxes muscle
Dysmenorrhea (p 2561)	Relaxes smooth muscle
Headache (p 1512)	Antihistaminic effect (?)
Motion sickness (p 1487)	Dramamine (100 mg tablets) specific for prevention and palliation
Morphine addiction (p 3861)	Reduces severity of withdrawal symptoms
Paralysis agitans (p 1505)	Reduces tremor when given with scopolamine etc
Radiation sickness (p 3798)	Try as prophylactic and palliative
Streptomycin toxicity (p 4610)	Reduces incidence and severity of eighth nerve damage
Angina pectoris (p 890)	Said to be palliative
Acute nephritis (p 179)	Seems to speed recovery in poststreptococcal nephropathies
Common cold (p 391)	Reduces local discomfort in those with bacterial hypersensitivity
Tuberculosis (p 4597)	Under investigation for possible synergistic efficacy with antibiotic

ANTI INFECTIVE THERAPY

In 1932 first reports of successful sulfonamide treatment of human infectious disease inaugurated an era to which future medical historians may refer as 'The Golden Age of Therapeutics In the few years that have elapsed between that momentous date and preparation of this Progress Volume accomplishments in the fields of anti infective therapy have transcended in their importance the sum of all previous contributions

The following brief historical survey is intended primarily for broad orientation It may serve also to caution practitioners that continued and continuing progress preclude dependence upon static therapeutic routines Alert attention to current medical research is required of those who strive to make readily available to their patients the boons of pending innovations

The various anti infective agents such as arsenicals antibiotics sulfonamides etc are discussed separately and will be found in alphabetical order

EARLY ANTI INFECTIVE TREATMENT (1796)

Prior to the early nineteenth century the great pioneer contributions to medicine were essentially of diagnostic significance After the contagious nature of certain diseases was established, many specific bacteria were later identified as causative agents in clinically definitive syndromes

Unfortunately these diagnostic triumphs were for the most part therapeutically infertile Indeed, the first eighteen hundred years A.D recorded only two significant dates in the development of anti infective treatment. In 1638 the Countess of Chinchon, living on a Pacific island off the coast of Peru was cured of an attack of fever presumably malaria by administration of a decoction prepared from cinchona bark the active ingredient of which was undoubtedly quinine and on May 13 1796 the immortal Jenner following the precepts of Lady Montagu inoculated a small boy with matter from vesicles of cowpox and later was able to demonstrate (July 1796) that the youngster had been rendered immune to smallpox

MIDDLE AGES OF ANTI INFECTIVE TREATMENT (1796–1894)

The hundred years that followed Jenner s discovery added three notable contributions to the annals of anti infective therapy In 1885 Louis Pasteur inoculated a child, bitten by a rabid dog with attenuated Rabies Vaccine in 1890 Behring and Kitasato prepared Antitoxic Serum for neutralization of soluble tetanus toxin and, in 1894 Pfeiffer developed an Antibacterial Serum to combat invaders that do not secrete soluble toxin. Thus at the advent of the twentieth century there had been established the principles of chemotherapy and vaccine therapy and of serotherapy with antitoxic and antibacterial products

DAWN OF THE GOLDEN AGE OF THERAPEUTICS (1894–1932)

The thirty-eight years which intervened between Pfeiffer s contribution and first reports (1932) of clinical use of sulfonamide were richer in promise than accomplishment On the positive side the most notable achievement was the epochal discovery of salvarsan the six hundred and sixth product prepared by Ehrlich in his search for a chemical to sterilize blood. For his experimental infectious disease Ehrlich chose syphilis but he expressed the hope that there might be found, for each individual infection, a sterilizing chemical of sufficient potency to kill invading micro-organisms without inflicting too serious damage on the tissues of the host.

During these dawn years Ehrlich s contributions to chemotherapy did not stand alone Vaccine and serum therapies were extended, antimeningococcus and type-

specific antipneumococcus serums were perfected By standards of their day these anti infective agents were accounted major therapeutic triumphs No contemporary would have believed that in the year 1950 they would already be obsolete

In contrast to the accomplishments of the Dawn Period there were bitter disappoint ments Ehrlich s vision of sterilatio magna was not translated into terms of reality for the blood in syphilis did not clear after a single injection of salvarsan. It became necessary to devise longer and longer courses of antisyphilitic treatment until, finally the Cooperative Clinical Group laid down a minimum plan of eighteen months of therapy Not only was arsenotherapy less efficacious than was originally reckoned but host toxicity proved more menacing Clinicians reported immediate and delayed unto- ward responses that varied in importance from minor discomforts to fatalities Newer arsenicals reputedly of greater therapeutic efficacy and lesser toxic potential were devised But the goal of the magic bullet was never attained, it was not possible to eliminate idiosyncrasy to and poisoning by ar enic

Despite these shortcomings arsenotherapy of syphilis was the most successful of chemotherapeutic contributions Other chemical substances hopefully prepared to combat various bacterial invaders were lethal in the test tube (*in vitro*) but curiously inactive after introduction into the body (*in vivo*)

In like manner treatment with vaccines and most serums revealed deterrents Vac cines and most antitoxic serums were demonstrably useful in prophylaxis but disap- pointing in active treatment of disease Technical difficulties limited the use of heterologous antitoxic and antibacterial serums intravenous injections of considerable bulk proved too cumbersome for routine use in the office or the home of the patient; additionally the occurrence of unpredictable anaphylactic and allergic reactions added so grievously to treatment risk that many practitioners feared to employ these anti infective agents in their private practices

To the disappointment of the Dawn Period must be added the record of two lost opportunities of tragic magnitude In 1908 Paul Gelmo prepared sulfanilamide for the German dye industry This accomplishment was reported and filed—and then for gotten for a quarter century In 1929 penicillin the most powerful and least toxic anti infective agent was described and isolated Nevertheless for more than a decade following Fleming s epochal di covery this giant among therapeutic preparations was used only to ensure the growth of penicillin resistant organisms in bacterial culture mediums In their classic monograph on penicillin Anderson and Keefer state It is remarkable to recall that penicillin was administered to a patient in this country (United State of America) for the fir t time only five years ago (1942) and that only two years ago (1945) were the difficulties of producing the drug overcome to the extent that its sale and distribution could be freed of all limitations and regulations

The meager therapeutic harvest of these years (1894–1932) is best reflected in stand ard texts of the period Thus Allbutt and Rolleston (A System of Medicine Macmillan 1905) listed forty seven common infectious diseases For thirty two of these (approxi mately 70%) only symptomatic or supportive therapy was recommended prophy lactic vaccination, efficacious by present standards was available for five (typhoid fever cholera plague smallpox and rabies) antitoxic serum for three (tetanus diph theria and scarlet fever) antibacterial serum for two (anthrax and bacillary dysentery) and the roster of chemotherapeutic agents included only quinine for malaria ipecac for amebic dysentery salicylate for rheumatic fever and mercury and iodides for syphilis

Seven years later Osler and MacCrae (Modern Medicine Lea and Febiger 1913) added antimeningococcus serum as the single significant contribution of the period that elap ed between publication of the English multivolume standard text and its American counterpart (By this time sulfanilamide had already re ted on the shelf for five years!)

Twenty five years later in the thirteenth edition of Osler s one volume Principles and Practice of Medicine (Appleton Century 1938) three decades after Gelmo syn thesized sulfonamide and almost a decade after the discovery of penicillin Dr Henry Christian could supplement the list of u eful anti infective agents with only the following

1 Arsenic for the treatment of spirochetal diseases including syphilis
2 Antimony for lymphopathia venereum and leishmaniasis
3 Quinacrine and plasmochin, for malaria
4 Several newer drugs for amebic dysentery

5 Germanin, for trypanosomiasis
6 Vaccines for whooping cough and glanders
7 Type specific antipneumococcus serums
8 Immune convalescent serums for whooping cough measles and poliomyelitis
9 A total of forty-eight lines devoted to sulfanilamide· of these twenty two described its toxicity and twenty-eight its therapeutic value
10 Concerning penicillin, *not even a listing*

Of these addenda already obsolescent are sulfanilamide immune convalescent serums type specific antipneumococcus serum quinacrine and plasmochin, in malaria and antimony in lymphopathia venereum. And arsenotherapy has been relegated to an ancillary status in the treatment of treponematoses

THE GOLDEN AGE OF THERAPEUTICS PERIOD I (1932–1946)

The Golden Age of Therapeutics was born unobtrusively in 1932 when Domagk demonstrated the clinical value of sulfanilamide It was not until 1935 however that there appeared more than an occasional case report. Even the texts of 1938 as detailed in previous paragraphs contained only sketchy and tentative references to the most potent anti infective agent that had been, up to this time in medical history acquired by man.

Beginning with 1940 the medical literature was flooded with reports of sulfonamide miracles The list of conquered or conquerable diseases was lengthened to include those caused by staphylococci streptococci pneumococci meningococci gonococci V comma (cholera) H ducreyi (chancroid) and H influenzae Even therapeutic nihilists succumbed to evidence that unfolded before their eyes and the term specific took on new meaning in therapeutics

Chemists produced new soluble and insoluble sulfonamide derivatives pharmaceutical laboratories prepared tablets solutions drops ointments suppositories and salves bacteriologists classified sensitive and resistant organisms clinical pathologists devised tests for determining levels in blood urine spinal and other tissue fluids clinicians reported on the variety of infectious diseases which responded or which failed to respond, to sulfonamides administered orally subcutaneously intramuscularly intravenously intraperitoneally and intrathecally· warnings were issued as to toxicity· methods were devised for control of the drug and protection of the patient and particular indications for use of antibiotic in specialist fields were given by surgeons ophthalmologists otologists rhinologists gynecologists obstetricians neurologists urologists dermatologists laryngologists gastro enterologists and pediatrists

Even while the first of these momentous therapeutic accomplishments was being recorded Chain and the Floreys (1940) were preparing to report on the therapeutic efficacy of penicillin in the treatment of human disease It soon became obvious that the practically non toxic penicillin was effective against many sulfonamide sensitive organisms such as staphylococci streptococci pneumococci meningococci and gonococci But the new antibiotic also could be employed successfully in sulfonamide resistant invasions including tetanus gas gangrene anthrax, diphtheria and the treponematoses most particularly syphilis Thus sulfanilamide forgotten on a shelf for more than twenty five years and hailed as the wonder drug in 1935 within a period of five years was being superseded for many of its indications by penicillin

The harvest of the First Period of the Golden Age transcended even the miracles of sulfonamide and penicillin In 1942 para aminobenzoic acid was revealed as a near specific in the treatment of rickettsial infections (Snyder Maier and Anderson) Oral administration of this new anti infective agent hastened recovery in formidable diseases such as typhus Rocky Mountain spotted and tsutsugamushi fevers

Progress also was reported in the use of antimalarials anti amebics and other anti protozoans quinine was variously being replaced by or supplemented with quinacrine (atabrine) pentaquine (SN 13276) isopentaquine chloroquine (aralen SN 7618) and chlorguanide (paludrine SN 12837) emetine first introduced in 1912 as an anti amebic agent was being replaced by or supplemented with chiniofon (1921) acetarsone (1924) vioform (1931) and carbarsone (1931) the antiprotozoal activity of antimony compounds became more clearly established and the National Formulary approved of trivalent and pentavalent compounds including stibophen stibamine and ethylstibamine

Finally to crown the accomplishments of these crowded years Waksman, Schatz and Bugie isolated streptomycin (1944) To the list of invasions that responded to anti infective therapy now were added many urinary infections colon bacteremia whooping cough H influenzal meningitis brucellosis tularemia Klebsielloses and certain types of tuberculosis

Reflecting the momentous advances of the first fifteen years of the Golden Age of Therapeutics the second printing (1947) of The Integrated Practice of Medicine listed ninety nine specific infections In these effective prophylaxis was available for eighteen effective active treatment, by serum or vaccine for two effective treatment with anti infective agents for sixty-one

In contrast to the 70 per cent of infections for which only supportive or symptomatic therapy was described in the texts of 1905 and 1908 it was now possible to claim control or cure for 71 per cent of diseases due to invasion by living micro-organisms!

THE GOLDEN AGE OF THERAPEUTICS PERIOD II (1946–1950)

The four years which have elapsed between publication of the first edition of The Integrated Practice of Medicine (1946) and this current Progress Volume (1950) have seen further advances in anti infective therapy In 1947 Burkholder announced the discovery of chloramphenicol (chloromycetin) and Duggar of aureomycin With the advent of these preparations para-aminobenzoic acid became obsolescent in the treatment of rickettsial disease and the roster of di eases which respond to the antibiotics again lengthened to include rickettsioses typhoid fever almonelloses (the paratyphoid fevers) shigelloses (bacillary dysentery) psittacosis granuloma inguinale lymphopathia venereum brucello is and virus pneumonitis

And the end is not yet! In 1949 Waksman added to his laurels by preparing neomycin and dihydrostreptomycin to supplement or perhaps to replace streptomycin, and there began to appear preliminary reports of newer antibiotics including polymyxin aerosporin bacillomycin, suramin para amino salicylic acid, subtilin antryptol terramycin etc

* *

Thus medical science almost impotent against invasion by living micro organisms up to the beginning of the 20th century succeeded in its conquest of coccal bacillary treponemal rickettsial and amebic invasions as well as many protozoal and helminthic diseases Only the viruses remained as a challenge and their ranks began to crumble with the surrender of virus pneumonitis and lymphopathia venereum to aureomycin and chloramphenicol In a period when the atomic physici t had unwillingly given civilization its most lethal weapon medicine gained almost complete mastery over microbial invasions of the human body!

ANTIMALARIALS

[See under Malaria (p 4392)]

ANTIMONIALS

Interest in the antimonials has been stimulated by introduction of less toxic preparations of proven parasiticidal efficacy

Available Products

Trivalent pentavalent and aromatic diamidine preparations of antimony are available Trivalent products appear most efficacious in the treatment of schistosomiasis and filariasis pentavalent in systemic leishmaniasis (kala azar) and aromatic diamidines for tumor inhibiting properties in multiple myeloma In each category experts express differences of opinion as to the preparation of choice hence the practitioner is confounded by multiple conflicting recommendations Under these circumstances the least toxic product warrants trial under rigid precautions

Therapeutics

The local use of antimonials has been abandoned Tartar emetic is no longer employed as pustulant emetic nauseant and expectorant

After absorption antimony compounds are of clinical value in the treatment of infections due to certain bacteria fungi viruses trypanosomes and helminths Additionally antimony may possess tumor inhibiting properties as best illustrated in multiple myeloma

Because of its toxicity antimony yields preference to more benign anti infective agents as illustrated by substitution of suramin in trypanosomiasis and of aureomycin in lymphopathia venereum and granuloma inguinale

However in the presence of definitive indications for therapy with antimony the accompanying table lists preferences that appear best suited to the requirements of the practitioner whose first consideration must be prevention of host toxicity (noli nocere) As to the preferred route of administration oral preparations are irritating and so poorly absorbed that their therapeutic benefits are almost completely nullified intramuscular deposits decrease efficacy but are preferred to intravenous injections which have added toxicity

THERAPEUTICS OF ANTIMONIALS

Preparation	Indications	Comments
TRIVALENT		
Anthiolimine (Lithium Antimony thiomalate) 6% solution	Filariasis	Prefer hetrazan and ethylstibamine
	Mucocutaneous leishmaniasis	Prefer ethylstibamine or stibophen. Use initial probatory intramuscular injection of 1 5 cc Follow by 3 cc daily for 1 month.
Antimony and Sodium Tartrate B P		Prefer U S P Sodium Salt
Antimony and Potassium Tartrate U S P (Tartar Emetic) ampuls 5 cc of 1% (Abbott, Lilly Parke Davis)	Granuloma inguinale	Prefer aureomycin or ethylstibamine
	Mucocutaneous leishmaniasis	Prefer stibophen
	Lymphopathia venereum	Prefer aureomycin.
	Schistosomiasis	Choice with stibophen and ethylstibamine Most experts prefer intravenous injections of freshly prepared 2% solution in sterile distilled

THERAPEUTICS OF ANTIMONIALS (*Continued*)

Preparation	*Indications*	*Comments*
		water After probatory dose of 1 cc increase by daily increments of 1 cc to total 5 cc Continue daily injections of 5 cc to total 90 cc unless toxicity occurs
Antimony Thioglycollamide U S P (Hynson) 0 4% in 10 and 20 cc ampuls		Prefer less toxic antimony sodium thioglycollate
Antimony Sodium Thioglycollate U S P (Hynson) 0 5 in 10 and 20 cc ampuls	Filariasis	Prefer hetrazan and ethylstibamine
	Granuloma inguinale	Prefer aureomycin.
	Schistosomiasis	*Prefer stibophen*
	Trypanosomiasis	Prefer suramin.
		Inject intravenously 10 to 20 cc every third day for 15 to 25 doses to total 150 to 500 cc unless toxicity occurs
Diramin (Parke Davis) (2%)	Granuloma inguinale	Prefer aureomycin.
	Mucocutaneous leishmaniasis	Prefer stibophen or ethylstibamine
		After initial probatory intravenous injection of 1 cc increase to 2 cc and give every other day for 5 to 15 doses
Fuadin See Stibophen		
Lithium Antimony Thiomalate See Anthiolamine		
Neostimosan See Stibophen		
TRIVALENT		
Stibophen N.F (Neostimosan Fuadin) (Winthrop) 6 3% in 5 cc ampuls	Mucocutaneous leishmaniasis	First choice
	Schistosomiasis	First choice with tartar emetic and ethyl tibamine
		For initial probatory intramuscular injection give 1 5 cc Increase to 3 5 cc the second day and to maximum dose of 5 cc on the third day Thereafter give 5 cc every day to total 40 cc To prevent relapse repeat 5 cc once weekly for two months Course may be repeated after ten-day rest.
Tartar Emetic See Antimony and Potassium Tartrate		
PENTAVALENT		
Ethylstibamine (Bayer 693 Neostibosan) (Winthrop) 0 3 gm. in ampuls	Systemic leishmaniasis (*Kala Azar*)	*First choice*
	Filariasis	Choice after hetrazan.
	Schistosomiasis	First choice

THERAPEUTICS OF ANTIMONIALS (*Continued*)

Preparation	Indications	Comments
	Granuloma inguinale	Prefer aureomycin.
	Paragonimiasis	Choice after emetine Add 6 cc of sterile diluent to make 5% solution for intra venous use Inject 4 cc for initial probatory dose If no toxi city increase to 6 cc and give daily for ten to seventeen days Add 1.2 cc of sterile diluent for intramuscular use Inject 0 2 cc for initial probatory dose par ticularly for infants and children If tolerated, increase daily by increments of 0 2 cc to 1 2 cc for adults unless toxicity occurs earlier
Neostam See Stibamine glucoside		
Neostibosan See Ethylstibamine		
Solustibosan (Bayer 561)		Not available
Stibamine Glucoside N N R (Neostam) (Bur roughs Wellcome Vials of 0 1 0 5 1 and 5 gm	Systemic leishmaniasis	Prefer Ethylstibamine Prepare a 4% solution by dis solving 100 mg in 2 5 cc sterile distilled water Inject intra venously or intramuscularly 2 5 cc per 100 pounds of body weight every second day for 30 injections (total 3 gm per 100 pounds)
PENTAVALENT		
Stibamose		Not available
Stibatin		Not available
Stibosan		Not available
Urea stibamine		Not available Regarded as preparation of choice (Snapper) in systemic leishmaniasis After probatory intravenous doses of 50 100 and 150 mg in 10 cc distilled water give 200 mg every other day for 12 to 15 injections
AROMATIC DIAMIDINES		
Pentamidine (SN 9406)	Investigational use	May be less toxic than ethylstibamine
Phenamidine (SN 9404)	Investigational use	
Propamidine (SN 6)	Investigational use	
Stilbamidine	Investigational use	Trial in multiple myeloma Prepare a 1% solution in dis tilled water Inject intravenously 2 5 cc per 100 pounds of body weight Increase every second day by increments of 2 5 cc to total 15 cc per injection Try to give a minimum of 10 injections Course may be repeated after rest period of one month

Toxicology

Untoward responses to antimonials include immediate and delayed symptoms Most of the former are encountered with intravenous injection They include nau ea vomiting fall in blood pre sure syncope sweating diarrhea urticarias respiratory depression cough headache abdominal pain and convulsions Many of these are preventable by scrupulous attention to details of injection certain preparations (antimony potassium tartrate) must be freshly prepared sterile distilled water must be u ed as diluent ampuled products must not be heated and should be injected within a few moments after exposure to the air the vein must be cleanly negotiated so that there is no perivenous leakage injections must be given at an exceedingly slow rate (less than 1 cc per minute) since much of the immediate toxicology resembles the syndrome of speed shock (pp 924 3774)

Delayed toxic manifestations resemble those of arsenic poisoning (p 122) They include albuminuria hematuria oliguria and anuria suggesting renal irritation jaundice as a hepatotoxic manifestation toxicoderms (pp 122 3339) drug fever (p 24) arthralgias neurotoxic manifestations including headache peripheral neuritis and paresthesias blood dyscrasias such as leukopenia anemia and thrombocytopenia irritation of the gums as in bismuth poisoning (p 1677) and diarrhea Toxicology is usually variable but in general pentavalent preparations are least noxious followed by trivalent and then aromatic diamidines

Antidote

Injections of BAL (pp 767 4251) are antidotal as in arsenic poisoning (p 122)

ANTIRETICULAR CYTOTOXIC SERUM (ACS)

ACS is a Russian product prepared by Bogomolets and alleged to have efficacy in the treatment of arthropathies and malignancies

Available Products

There are no commercially available preparations of ACS

Therapeutics

ACS is recommended in an initial dose of 0 5 cc followed, at intervals of three to five days by doses of 1 cc and 1 5 cc A enes of three injections constitutes a complete course Second and third series may be given at six week intervals

American observers have noted no significant difference between a group of patients with rheumatoid arthritis treated with ACS and those given a neutral control serum

The alleged effects of ACS on wounds fractures malignancy pulmonary abscesses empyema septic infections adnexal disease puerperal fever gonorrheal peritonitis scarlet fever typhus rheumatic fever multiple sclerosis schizophrenia ozena etc appear no more promising to objective investigators than its efficacy in rheumatoid arthritis and *other arthropathies*

ANTIVENIN CROTALUS

[See Snakebite]

ANTIVENIN (LATRODECTUS MACTANS)

An antitoxic serum prepared by immunization of healthy horses against venom of black widow spiders

Available Products

Lyovac Antivenin N N R (Mulford Sharp & Dohme Wyeth) Pack age contains 1 cc vial of normal horse serum (1 10) for use in ophthalmic and intracutaneous tests of sensitivity ampul of 2 5 cc of sterile dis tilled water and vial containing sufficient amount of lyophilized anti venin to be the equivalent of 2 5 cc of restored double concentration antivenin when contents of ampul of distilled water are added

Therapeutics

[See Arachnidism p 4228]

ANTRYCIDE

Antrycide (4 amino 6 (2) amino 6 methylpyrimidyl-4-amino) quinal dine 1 1 dimetho) or M 7555 is a white crystalline powder soluble in water

Available Products

Antrycide a product of Imperial Chemical Industries is not yet available for human use (1950)

Therapeutics

A single injection of antrycide cures cattle of Trypanosoma congolense and Trypanosoma vivax infections It has al o been succe sful against Trypanosoma brucei infections in cattle horses and dogs against Try panosoma evansi in cattle and Trypanosoma simiae in pigs (p 4594)

In cattle experiments antrycide apparently protects against T con golense for six months In rare instances of recurrence second treat ments have proven satisfactory (J A M A 139 1017 1949)

Toxicology

Antrycide has no significant side reactions so far as is presently known

ARACHNIDISM

[Spider Bite Black Widow Bite]

Principles of Diagnosis and Treatment

1 With the exception of the product of the black widow (*Latrodectus mactans*) spider venoms produce only local discomfort and inflammation Even the hairy tarantula despite its vicious appearance does not introduce significant amounts of toxin into the body

2 The ordinary spider bite is allayed by application of wet dressings and administration of antihistamine locally and orally An ointment of 2% pyribenzamine (or any other preparation of similar activity) is rubbed vigorously into the area of the bite Additionally tablets of 50 mg of the antihistamine are given orally every hour until relief is afforded

3 In contrast to the ordinary spider bite the venom of the black widow is exceedingly toxic and may produce fatality Since the black widow thrives in moist dark places favorite sites for inoculation are the genitals of those who have used an outdoor privy or who have squatted in the great open spaces for purposes of evacuation

4 Within a few moments after being bitten the patient usually complains of intense local pain radiating to abdomen legs chest or back Shortly afterwards there may occur vomiting tremors of the hands fibrillary twitchings of face and neck headache precordial distress hyperesthesia of the soles of the feet sweating and respiratory difficulties Examination at this time may disclose fever hyperreflexia elevation of blood pressure tachycardia priapism a macular eruption and an abdomen so rigid as to suggest an acute surgical emergency In extreme instances the patient develops convulsions or becomes comatose and may rapidly succumb

5 There is available a potent antivenin for Latrodectus mactans although specific therapy is rarely employed due to (a) delay in obtaining the preparation during the brief period of the acute emergency and (b) the danger of hypersensitivity reactions following its introduction

Practical Management

Immediate Care

1 Give a slow intravenous injection of 10 to 20 cc of calcium gluconate Despite urgency of symptoms maximum rate of injection must be kept below 1 cc per minute since otherwise the patient may develop flushing and congestion due to injected drug Meantime send a member of the household for Lyovac Antivenin as marketed by Wyeth Mulford or Sharp & Dohme (p 4227)

2 With another syringe inject intramuscularly an opiate such as 100 mg of demerol or 1 mg of dilaudid

3 After injection of opiate or a substitute fill the syringe with 5 cc of 1% benadryl and administer antihistamine intramuscularly

4 While these injections are being given have a tub filled with hot water Prepare to immerse the patient as soon as possible

5 If symptoms have not been controlled by the combination of calcium opiate and warm bath inject intramuscularly 2 cc of neostig mine methylsalicylate (1 2000) together with atropine sulfate 0 5 mg (1/120 grain)

6 With persistence of discomfort repeat intravenous injection of calcium

7 Continuing to alternate calcium antihistamine opiate and neo stigmine determine relative sensitivity of the patient by history and by ophthalmic and cutaneous reactions to horse serum (p 554)

8 If patient is not hypersensitive restore lyophilized antivenin to a volume of 2 5 cc with diluent Inject intramuscularly unless symptomatic therapy has proven effectual

9 Immediately following serum injection give another 5 cc of 1% benadryl for antihistaminic effect

10 If relief has not been obtained repeat serum injections every fifteen to thirty minutes if necessary until the patient recovers or succumbs

11 In the hypersensitive individual with positive skin or eye tests try to avoid serum therapy unless the situation is desperate Under these circumstances attempt desensitization by intracutaneous injection of 0 1 cc of 1 100 dilution Every ten or fifteen minutes repeat the injec tion using increments of 0 1 cc until 1 cc of 1 100 solution has been administered After every second or third injection of serum give an additional 5 cc of 1% benadryl

12 When the patient can tolerate 1 cc of 1 100 dilution follow the same procedure with 1 10 dilution Start with 0 1 cc and increase by increments of 0 1 cc every ten or fifteen minutes until 1 cc of 1 10 dilution has been delivered

13 When patient has tolerated 1 cc of 1 10 dilution give 0 1 cc of undiluted antivenin Again increase by increments of 0 1 cc every ten or fifteen minutes until the total amount of 2 5 cc of undiluted antivenin has been injected

14 While desensitizing doses of antivenin are being injected in addition to a syringe containing 5 cc of 1% benadryl have ready another syringe containing 2 cc of epinephrine hydrochloride (1 1000) for use if emergency symptoms are encountered

15 Since the outcome of arachnidism is determined within the course of a few hours treatment must be persistent and unrelenting During the tedious process of desensitization an assistant continues symptomatic therapy using calcium gluconate intravenously and opiate antihistamine and neostigmine intramuscularly noting the response to each preparation and giving the largest possible doses that do not simultaneously produce toxic reactions or side effects

16 Because of rapid absorption of venom local incisions and suc tion have no value

17 In the event that sedation is not afforded by opiate and calcium salt give an intravenous injection of soluble barbiturate (0 5 gm of

sodium luminal) or of 20 cc of 10% magnesium sulfate If the latter is used another syringe with 10% calcium gluconate is kept available for administration as an antidote if respiratory depre sion is produced by the magnesium ion

ARSENICALS

Inorganic and organic arsenicals are available each as trivalent and pentavalent preparations

Trivalent Inorganic Arsenicals

Of *trivalent inorganic arsenicals only liquor potassii arsenitis* (Fowler s solution) is used in modern clinical practice No longer pre scribed for what was vaguely called alterative action Fowler s solution is employed currently in leukemia for leukocytic effects similar to those produced by radioactivity

Pentavalent Inorganic Arsenicals

Of pentavalent inorganic arsenicals sodium cacodylate is the sole survivor Cacodylate injections are used for their tonic effects Evidence of this alleged activity appears to rest primarily on the vet erinarian opinion that arsenic makes the horse s coat more sleek and silky

Piqures of cacodylate of soda retain great popularity on the con tinent but the boons that follow this type of arsenotherapy are more likely psychotherapeutic!

Trivalent Organic Arsenicals

Trivalent organic arsenicals notably Ehrlich s 606 were the magic bullets of the early twentieth century They found principal employment in the treatment of treponematoses especially syphilis

In the experiments that led to Massive Chemotherapy of Syphilis (p 344) it became undeniably clear to all but partisans that oxo phenarsine hydrochloride (mapharsen) was the organic trivalent arsen ical of choice (Table 15 p 124) Its advantages include ease of administration small bulk of diluent (2 cc) low effectual therapeutic dose *correspondingly low relative toxicity and high spirocheticidal* activity Since completion of Five day Treatment it appears that the more recently introduced dichlorophenarsine hydrochloride (clorarsen) shares the virtues of mapharsen However neither arsenical is com parable to penicillin as a safe and effectual spirocheticide

Pentavalent Organic Arsenicals

Pentavalent organic arsenicals may be sharing the fate of trivalent preparations Tryparsamide once hailed for its potency in neuro syphilis and trypanosomiasis *now is recognized as relatively ineffectual* in the first instance and as a preparation of relatively high toxicity in

the latter as compared with more newly introduced p-arsenosophenylbutyric acid and suramin sodium (p 4553)

INORGANIC ARSENICALS

TRIVALENT

Arsenic Trioxide U S P (arsenous acid, arsenous oxide)

Parent substance of trivalent arsenical Because of toxicity abandoned as tonic and alterative

Potassium Arsenite

Use as Liquor

Liquor Potassii Arsenitis (Fowler s Solution)

Obsolete as amebacide trypanocide tonic and hematinic Use for leukotoxic effects in leukemia (p 4262)

Solution Arsenous Acid

Obsolete

PENTAVALENT

Arsenic Acid

Parent substance of organic and inorganic pentavalent arsenicals High toxicity precludes therapeutic use

Cacodylate of Soda

Retains popularity as piqure for tonic and alterative action.

Solarson

Obsolete

ORGANIC ARSENICALS

TRIVALENT

Arsenoxide

See Oxophenarsine

Arsphenamine U S P (Salvarsan, 606)

First of the reasonably non toxic arsphenamines Because of its insolubility (25 cc for 100 mg) and its greater toxicity it has been superseded by oxophenarsine hydrochloride (mapharsen) and dichlorophenarsine hydrochloride (clorarsen)

Available Products Arsphenamine (Merck) Ampuls 0 1 0.2, 0 3 0 4 0 5 0 6 1 0 and 3 0 gm

Bismarsen

See Bismuth Arsphenamine

Bismuth Arsphenamine Sulfonate N.N.R (Bismarsen)

A derivative of arsphenamine containing bismuth (p 118) Bismarsen can not be recommended since it combines the hazards of an arsenical with those due to bismuth. The simpler bismuth subsalicylate in oil may be given for supplementary use if there appears to be an indication for bimetalism in therapeutics

Available Products Bismarsen (Abbott) Ampuls of 0 1 and 0 2 gm with ampuls of 0.25% butyn sulfate for use as diluent. For intramuscular use only

C C 914 C C 1037

See Carbarsone

Dichlorophenarsine Hydrochloride U S P (Clorarsen)

The most recently Council-accepted trivalent organic arsenical whose formula is 3 amino-4-hydroxyphenyl-dichloroarsine hydrochloride containing about 26% arsenic

Available Products Dichlorophenarsine hydrochloride (Abbott, Winthrop) Ampuls of 45 and 68 mg Clorarsen (Squibb) Ampuls 45 and 68 mg and Dichlor mapharsen (Parke Davis) Ampuls 50 and 75 mg

With oxophenarsine hydrochloride (mapharsen) clorarsen is the arsenical of choice in the treatment of syphilis On addition of as little as 2 cc of sterile distilled water solution is effected and arsenoxide is formed. Use in the manner and dosage of mapharsen.

sodium luminal) or of 20 cc of 10% magnesium sulfate If the latter is used another syringe with 10% calcium gluconate is kept available for administration as an antidote if respiratory depression is produced by the magnesium ion

ARSENICALS

Inorganic and organic arsenicals are available each as trivalent and *pentavalent preparations*

Trivalent Inorganic Arsenicals

Of trivalent inorganic arsenicals only liquor potassii arsenitis (Fowler s solution) is used in modern clinical practice No longer pre scribed for what was vaguely called alterative action Fowler s solution is employed currently in leukemia for leukocytic effects similar to those produced by radioactivity

Pentavalent Inorganic Arsenicals

Of pentavalent inorganic arsenicals sodium cacodylate is the sole survivor Cacodylate injections are used for their tonic effects Evidence of this alleged activity appears to rest primarily on the vet erinarian opinion that arsenic makes the horse s coat more sleek and silky

Piqures of cacodylate of soda retain great popularity on the con tinent but the boons that follow this type of arsenotherapy are more likely psychotherapeutic!

Trivalent Organic Arsenicals

Trivalent organic arsenicals notably Ehrlich s 606 were the magic bullets of the early twentieth century They found principal employment in the treatment of treponematoses especially syphilis

In the experiments that led to Massive Chemotherapy of Syphilis (p 344) it became undeniably clear to all but partisans that oxo phenarsine hydrochloride (mapharsen) was the organic trivalent arsen ical of choice (Table 15 p 124) Its advantages include ease of administration *small bulk of diluent (2 cc) low effectual therapeutic* dose correspondingly low relative toxicity and high spirocheticidal activity Since completion of Five day Treatment it appears that the more recently introduced dichlorophenarsine hydrochloride (*clorarsen*) shares the virtues of mapharsen However neither arsenical is com parable to penicillin as a safe and effectual spirocheticide

Pentavalent Organic Arsenicals

Pentavalent organic arsenicals may be sharing the fate of trivalent preparations Tryparsamide once hailed for its potency in neuro syphilis and trypanosomiasis now is recognized as relatively ineffectual in the first instance and as a preparation of relatively high toxicity in

CC 914 CC 1037

Trivalent analogs of carbarsone (V.S) Comparison between the two thioarsenites indicates that each is effective and there is little difference in the response to them. Except for nausea and vomiting there were no evidences of toxicity due to the drug and these manifestations were eliminated by coating with phenyl salicylate

Dose levels of from 1/8 to 1/4 those required for carbarsone U S P are effective in human beings Enteric coated tablets provide a useful form especially for ambulatory patients The drugs are equally effective against motile or encysted forms and effective drug levels can be developed in the liver and tissues of the bowels where they are needed

Fourneau 270

See Tryparsamide

p-Arsenophenylbutyric Acid

An acid substitute phenyloxide for investigational use in the treatment of trypanosomiasis Daily injections of 0 5 mg per kg of body weight for two weeks or of 1 mg per kg for one week are under current clinical trial in trypanosomiasis Para-arsenosophenylbutyric acid apparently has negligible toxicity in the doses used (p 4595)

Phenarsone Sulfoxylate N.N R (Aldarsone)

Sodium 3-amino-4 hydroxyphenylarsonate N methanol sulfoxylate It is a pentavalent arsenical (p 120) containing about 18% arsenic

Available Products Aldarsone (Abbott) Ampuls of 0 5 gm. and 1 gm. Aldarsone (Abbott) Vaginal Suppositories 0 5 gm

In neurosyphilis prefer penicillin and/or mapharsen or clorarsen, in amebic dysentery carbarsone is more efficient and less toxic in trichomonas vaginalis prefer less toxic trichomonicides

Sodium Arsanilate (Atoxyl)

An early preparation of organic pentavalent arsenical Superseded by less toxic products.

Stovarsol

See Acetarsone

Tryparsamide (Fourneau 270)

Obsolete and dangerously toxic pentavalent organic arsenical yielding to penicillin and the less toxic arsenicals mapharsen and clorarsen in the treatment of syphilis to cloroquine and chlorguanide in malaria and to suramin sodium (naphuride) in trypanosomiasis

Toxicology

The toxicology of arsenic remains unchanged (pp 122–125 Fig 16 p 123) although its threat has been significantly lessened through the introduction of BAL as an effectual antidote

Antidote

British Anti Lewisite (BAL) N N R (p 4251) is especially useful in the treatment of arsenical encephalopathies (p 124) toxicoderms (Fig 16 p 123) and agranulocytoses (p 1096)

Despite the extraordinary antidotal properties of BAL arsenotherapy cannot approach penicillin as a safe modality in the treatment of syphilis and allied infections It remains to be demonstrated whether combined arsenic and penicillin therapy will yield results sufficiently superior to those obtained with penicillin alone so that the hazard of arsenical poisoning is justified even granting the le sening risk through availability of BAL

Mapharsen
See Oxophenarsine

Neoarsphenamine U S P (Neosalvarsan)
Virtually obsolete trivalent organic arsenical superseded by oxophenarsine hydrochloride (mapharsen) and dichlorophenarsine hydrochloride (clorar sen) in the modern treatment of syphilis (p 4554) and allied trepone matoses (p 331)
Available Product Neoarsphenamine (Abbott, Merck Squibb) Ampuls 0 15 0 3 0 45 0 6 0 75 0 9 3 0 and 4 5 gm Compare cumbersome technic (p 117) with simplicity of administration of mapharsen and clorarsen (p 119)

Oxophenarsine Hydrochloride U S P (Arsenoxide Mapharsen)
The preferred trivalent organic arsenical (p 119) with dichlorophenarsine hydrochloride (clorarsen) in the modern treatment of syphilis (p 345)
Available Product Mapharsen (Parke Davis) Ampuls 40 and 60 mg For ease of administration (p 119) safety and efficiency the arsenical of choice in private practice (p 4554)

Silver Arsphenamine N N R.
Obsolete organic trivalent arsenical (p 4230) yielding to less toxic oxophenarsine hydrochloride (mapharsen) and dichlorophenarsine hydrochloride (clorar en) in the modern treatment of syphilis

Sulfarsphenamine U S P
Obsolete trivalent organic arsenical yielding to oxophenarsine hydrochloride (mapharsen) and dichlorophenarsine hydrochloride *(clorarsen) in the* modern treatment of syphilis

PENTAVALENT

Acetarsone N F (Stovarsol)
3 acetylamino-4 hydroxyphenyl 1 arsenic acid containing 27% organic penta valent arsenic
Available Products Tablets Acetarsone (Abbott) 100 and 250 mg tablets stovarsol (Merck) 25 50 and 100 mg acetarsone powder for vaginal *insufflation 500 mg (12 5% acetar one with equal parts of kaolin* and sodium bicarbonate)
In amebic dysentery acetarsone has greater toxic potential than oxyquinolines rated less desirable arsenical than carbarsone
In trichomonas vaginalis acetarsone has greater toxic potential than oxy quinolines (p 4592)

Acetylarsan
A diethylamine of pentavalent acetarsone (stovarsol) Superseded as anti syphilitic by organic trivalent arsenicals such as the hydrochlorides of oxophenarsine (arsenoxide mapharsen) and dichlorophenarsone (clorarsen)

Aldarsone
See Phenarsone

Atoxyl
See Sodium Arsenilate

Carbarsone U S P
A pentavalent arsenical (4 ureido 1 phenyl arsonic acid) containing about 28% arsenic
Available Products Carbarsone Powder (Lilly)—2 gm vial Carbarsone Tablets (Lilly)—50 and 250 mg Carbarsone Suppositories *(Lilly) 130 mg* Carbarsone Pulvules (Lilly)—250 mg
In amebic dysentery carbarsone is the choice of pentavalent arsenicals However detoxification of carbarsone oxide by sulfhydril groups has produced at least two thioarsenites presently referred to as C C 914 and C C 1037 which appear more effective and less toxic If original findings are sustained these trivalent analogs may replace carbarsone as an amebacide (p 4182)

CC 914 CC 1037

Trivalent analogs of carbarsone (V.S.) Comparison between the two thioarsenites indicates that each is effective and there is little difference in the response to them. Except for nausea and vomiting there were no evidences of toxicity due to the drug and these manifestations were eliminated by coating with phenyl salicylate

Dose levels of from $\frac{1}{16}$ to $\frac{1}{4}$ those required for carbarsone U.S.P. are effective in human beings. Enteric coated tablets provide a useful form, especially for ambulatory patients The drugs are equally effective against motile or encysted forms and effective drug levels can be developed in the liver and tissues of the bowels where they are needed

Fourneau 270

See Tryparsamide

p-Arsenophenylbutyric Acid

An acid substitute phenyloxide for investigational use in the treatment of trypanosomiasis Daily injections of 0 5 mg per kg of body weight for two weeks or of 1 mg per kg for one week are under current clinical trial in trypanosomiasis Para-arsenosophenylbutyric acid apparently has negligible toxicity in the doses used (p 4595)

Phenarsone Sulfoxylate N.N.R. (Aldarsone)

Sodium 3-amino-4 hydroxyphenylarsonate N methanol sulfoxylate It is a pentavalent arsenical (p 120) containing about 18% arsenic

Available Products Aldarsone (Abbott) Ampuls of 0 5 gm. and 1 gm., Aldarsone (Abbott) Vaginal Suppositories 0 5 gm.

In neurosyphilis prefer penicillin and/or mapharsen or clorarsen, in amebic dysentery carbarsone is more efficient and less toxic in trichomonas vaginalis prefer less toxic trichomonicides

Sodium Arsanilate (Atoxyl)

An early preparation of organic pentavalent arsenical Superseded by less toxic products

Stovarsol

See Acetarsone

Tryparsamide (Fourneau 270)

Obsolete and dangerously toxic pentavalent organic arsenical yielding to penicillin and the less toxic arsenicals mapharsen and clorarsen in the treatment of syphilis to cloroquine and chlorguanide in malaria and to suramin sodium (naphuride) in trypanosomiasis.

Toxicology

The toxicology of arsenic remains unchanged (pp 122–125 Fig 16 p 123) although its threat has been significantly lessened through the introduction of BAL as an effectual antidote

Antidote

British Anti Lewisite (BAL) N N R (p 4251) is especially useful in the treatment of arsenical encephalopathies (p 124) *toxicoderms* (Fig 16 p 123) and agranulocytoses (p 1096)

Despite the extraordinary antidotal properties of BAL arsenotherapy cannot approach penicillin as a safe modality in the treatment of syphilis and allied infections It remains to be demonstrated whether combined arsenic and penicillin therapy will yield results sufficiently superior to those obtained with penicillin alone so that the hazard of arsenical poisoning is justified even granting the lessening risk through availability of BAL

Mapharsen
See Oxophenarsine

Neoarsphenamine U S P (Neosalvarsan)
Virtually obsolete trivalent organic arsenical superseded by oxophenarsine hydrochloride (mapharsen) and dichlorophenarsine hydrochloride (clorarsen) in the modern treatment of syphilis (p 4554) and allied treponematoses (p 331)
Available Product Neoarsphenamine (Abbott Merck Squibb) Ampuls 0 15 0 3 0 45 0 6 0 75 0 9 3 0 and 4 5 gm Compare cumbersome technic (p 117) with simplicity of administration of mapharsen and clorarsen (p 119)

Oxophenarsine Hydrochloride U S P (Arsenoxide Mapharsen)
The preferred trivalent organic arsenical (p 119) with dichlorophenarsine hydrochloride (clorarsen) in the modern treatment of syphilis (p 345)
Available Product Mapharsen (Parke Davis) Ampuls 40 and 60 mg For ease of administration (p 119) safety and efficiency the arsenical of choice in private practice (p 4554)

Silver Arsphenamine N N R
Obsolete organic trivalent arsenical (p 4230) yielding to less toxic oxophenarsine hydrochloride (mapharsen) and dichlorophenarsine hydrochloride (clorarsen) in the modern treatment of syphilis

Sulfarsphenamine U S P
Obsolete trivalent organic arsenical yielding to oxophenarsine hydrochloride (mapharsen) and dichlorophenarsine hydrochloride (clorarsen) in the modern treatment of syphilis

PENTAVALENT

Acetarsone N F (Stovarsol)
3 acetylamino-4 hydroxyphenyl 1 arsenic acid containing 27% organic pentavalent arsenic
Available Products Tablets Acetarsone (Abbott) 100 and 250 mg tablets stovarsol (Merck) 25 50 and 100 mg acetarsone powder for vaginal insufflation 500 mg (12 5% acetarsone with equal parts of kaolin and sodium bicarbonate)
In amebic dysentery acetarsone has greater toxic potential than oxyquinolines rated less desirable arsenical than carbarsone
In trichomonas vaginalis acetarsone has greater toxic potential than oxyquinolines (p 4592)

Acetylarsan
A diethylamine of pentavalent acetarsone (tovarsol) Superseded as antisyphilitic by organic trivalent arsenicals such as the hydrochlorides of oxophenarsine (arsenoxide mapharsen) and dichlorophenarsone (clorarsen)

Aldarsone
See Phenarsone

Atoxyl
See Sodium Arsenilate

Carbarsone U S P
A pentavalent arsenical (4 ureido 1 phenyl arsonic acid) containing about 28% arsenic
Available Products Carbarsone Powder (Lilly)—2 gm vial Carbarsone Tablets (Lilly)—50 and 250 mg Carbarsone Suppositories (Lilly) 130 mg Carbarsone Pulvules (Lilly)—250 mg
In amebic dysentery carbarsone is the choice of pentavalent arsenicals However detoxification of carbarsone oxide by sulfhydril groups has produced at *least two thioarsenites presently referred to as* C C 914 and C C 1037 which appear more effective and less toxic If original findings are sustained, these trivalent analogs may replace carbarsone as an amebacide (p 4182)

AMINO ACIDS AND PROTEIN HYDROLYSATES FOR ORAL AND TUBE FEEDING

Product and Manufacturer	Comment
Amigen (Mead) N N R	For oral or tube feeding make 10–40% solution with water or fruit juice
Aminoids (Arlington)	One ounce (30 gm) provides approximately 12 gm protein hydrolysate and 12 gm carbohydrate to yield 100 calories
Casec (Mead)	Milk protein 88% fat 2% minerals 4 5% Each ounce yields 105 calories
Casein Hydrolysate (Squibb)	From enzymatic digestion of casein (85% protein) As Casec
Choline Chloride (Abbott, Upjohn)	Amino acid preparation. Each ounce yields 4 gm. choline chloride Lipotropic principle reverses fatty infiltration of liver and protects hepatic cells.
Choline Dihydrogen Citrate (Parke Davis)	Tablets 0 65 gm As choline chloride Give 4 tablets daily with fluid.
Delcos (Sharp & Dohme)	Palatable milk derivative Give 100 gm daily (50 gm protein and 30 gm carbohydrate)
Essenamine (Winthrop)	Lactalbumin hydrolysate As Casec
Ledinac (Lederle)	Liver protein hydrolysate with 38% maltose and vita min and mineral supplements (chocolate flavored) One ounce yields 100 calories
Lonalac (Mead)	A low sodium food containing 38% lactose 28% milk fat and 27% casein with minerals and added B vita min Supplies 500 calories per 100 gm.
Meonine (Wyeth)	Tablets 0 5 gm Lipotropic amino acid as choline above Give 6 to 12 tablets daily with high protein high vita min diet.
Methionine D (Abbott, National, Squibb etc)	Tablets 0 5 gm. as meonine above
Nutragest (Burroughs Wellcome)	Hydrolysates of casein, lactalbumin and yeast with 48 5% added carbohydrate vitamins and minerals
Protenum (Mead)	High protein, low fat food with 46% carbohydrate 42% protein, 7% minerals 3% moisture and only 2% fat. The energy yield of 100 gm is 370 calories
Protolysate (Mead) N N R	Casein hydrolysate One ounce yields nitrogen equivalent of 25 gm protein

Oral Feeding

Protein hydrolysates may be taken in water milk tomato or other vegetable juice or in a plain soup or bouillon Chilling the mixture by addition of chipped or crushed ice improves its palatability for many patients The method of preparation is simple

1 Pour required amount of fluid into a suitable vessel

2 Sprinkle prescribed amount of protolysate on surface Stir with fork or egg beater until powder is well dissolved

3 Add other ingredients

ARTIFICIAL FEEDING

Under certain circumstances usually trying patients cannot or will not maintain nutritive requirements by normal ingestion of fluids and foods Recourse must then be had to intragastric or transduodenal tube feedings or to intravenous infusions Commercial availability of amino acid and protein hydrolysates has greatly improved methods of artificial feeding

AMINO ACIDS

Indispensable amino acids include those which the body is unable to synthesize i e phenylalanine tryptophane methionine lysine leucine isoleucine threonine valine histidine and arginine The daily requirement of each individual amino acid varies between 0 3 and 5 gm ordinarily met on a diet that contains 70 gm of protein

Indications for use of individual amino acids include administration of glycine in myasthenia gravis (p 2882) histidine for peptic ulcer (p 1790) and methionine lysine and choline for lipotropic activity in cirrhosis of the liver (p 1969) Despite enthusiastic claims there is no evidence that prescription of pure amino acids accomplishes anything that cannot be accomplished by proper use of naturally occurring dietary proteins The latter are more easily available and considerably less expensive

PROTEIN HYDROLYSATES

Whereas the Council of the American Medical Association has not given its stamp of approval to any preparation of individual amino acid it has sanctioned several protein hydrolysates prepared by various methods of artificial digestion These provide adequate amounts of essential amino acids or of polypeptides yielding these essentials Protein hydrolysates are available in powder form for oral administration or duodenal tube feeding and in sterile non pyrogenic non antigenic solutions for intravenous infusion

For ease of administration economy and safety oral or duodenal feedings are preferred to parenteral injection The products listed below are commercially available and resemble one another in that they supply protein hydrolysate Most are milk protein derivatives though ledinac is of hepatic origin and nutragest is partially derived from yeast Some (aminoids delcos ledinac nutragest) have added carbohydrate others (ledinac nutragest) have vitamin and mineral supplements For the most part the practitioner may disregard these chemical differences in favor of palatability as determined by the individual taste of the individual patient Certainly several products should be tested before renouncing oral or tube feedings in favor of parenteral injection

5 Warm formula to body temperature before feeding (This warm ing period will melt the cream which rises to the top during the refrig eration period)

PROTOLYSATE DOSAGE FOR VARIOUS PROTEIN REQUIREMENTS
TUBE FEEDING

		Mild Protein Depletion	Moderate Protein Depletion
Weight of Patient Lb	Normal Protein Allowance gm	Dosage of protolysate per day which will furnish 50% of amount of protein normally allowed	Dose of protolysate which will furnish entire amount of protein normally allowed
110	50	4 level tblsp protolysate and 3 level tblsp dextrose in 9 ounces of water	8 level tblsp protolysate and 6 level tblsp dextrose in 18 ounces of water
132	60	5 level tblsp protolysate and 4 level tblsp dextrose in 12 ounces of water	10 level tblsp protolysate and 8 level tblsp dextrose in 23 ounces of water
154	70	6 level tblsp protolysate and 5 level tblsp dextrose in 14 ounces of water	12 level tblsp protolysate and 10 level tblsp dextrose in 27 ounces of water
176	80	6½ level tblsp protolysate and 5 level tblsp dextrose in 15 ounces of water	13 level tblsp protolysate and 10 level tblsp dextrose in 30 ounces of water
198	90	7½ level tblsp protolysate and 6 level tblsp dextrose in 17 ounces of water	15 level tblsp protolysate and 12 level tblsp dextrose in 34 ounces of water
220	100	8 level tblsp protolysate and 6½ level tblsp dextrose in 18 ounces of water	16 level tblsp protolysate and 13 level tblsp dextrose in 37 ounces of water

These solutions furnish the equivalent of approximately 2 2 gm of protein and 20 calories to the ounce and represent approximate concentrations of 10% dextrose and 10% protolysate

Intravenous Infusions

The Council on Pharmacy and Chemistry of the American Medical Association has accepted several products for intravenous infusion of protein hydrolysate Thus far the stamp of approval has been given to no pure preparation of essential amino acid on the ground that hydroly ates yield building blocks indispensable to protein synthesis

Council requirements for accepted products include the following

1 Of the total nitrogen present 50% or more must be in the form of alpha amino nitrogen

2 Sufficient hydrolysis must be accomplished to reduce the non antigenicity of products for oral and intravenous use

3 Intravenous products must be sterile and free from pyrogens

4 Added carbohydrate is permissible

5 Added vitamins minerals etc are not considered presently acceptable

Indications Indications for parenteral injection of protein hydroly sate include correction of hypoproteinemia and maintenance of a posi tive nitrogen balance particularly when there is interference with ingestion digestion or absorption of food

4 After preparation of protolysate solution or recipe keep in refrigerator until ready for use Observe same precautions in handling and storage as for other perishable foods such as milk

TYPICAL RECIPES

Tomato Juice Cocktail

Protolysate	3 level tablespoonfuls
Tomato Juice	¾ measuring cupful

Mix and serve cold. This recipe furnishes the equivalent of about 18 gm of protein.

Tomato Soup

Protolysate	1½ level tablespoonfuls
Canned Tomato Soup	½ average (10 to 11 oz.) can
Water	4 tablespoonfuls

Mix and heat. Serve hot This recipe furnishes the equivalent of about 11 gm. of protein

Jellied Consomme

Protolysate	4 level tablespoonfuls
Canned Con omme	1 average (10 to 11 oz) can
Water	⅓ measuring cupful
Plain Gelatin	½ level tablespoonful

Add gelatin to water (cool) Heat over a slow flame with constant stirring or over boiling water until gelatin is dissolved Stir gelatin solution into consomme Add protolysate and stir until di solved. Pour into 4 custard cups Chill in refrigerator This recipe furnishes the equivalent of about 45 gm of protein or 11 gm per serving

Tube Feeding

Administration of protolysate by tube is frequently prescribed when the patient is unable to take sufficient food by mouth (p 4235) In the unconscious patient the danger of aspiration makes the method somewhat hazardous The tube is usually introduced by the nasal route and may be placed in stomach or duodenum The material to be in erted through the tube should be warmed to body temperature before administration The tube is left in place and regular feedings up to 7 fluid ounces in volume may be administered at two to four hour intervals Night tube feedings supplement dietary intake of food during the day

Tube feedings are contraindicated when esophageal varices are present as in cirrhosis of the liver

Jejunostomy Feeding

A mixture suitable for jejunostomy feeding yielding the equivalent of 195 gm protein 258 gm carbohydrate 48 gm fat and 2170 calories is prepared by adding 2 measuring cupfuls of protolysate 2 measuring cupfuls of dextri maltose and 1 measuring cupful of cream (20%) to 1 quart of water

1 Place protolysate and dextri maltose in a mixing bowl
2 Add warm water and stir until powders are dissolved
3 Add cream Mix thoroughly
4 Boil formula for one minute Cool and store in refrigerator

FLUIDS FOR INTRAVENOUS INFUSIONS (p 3775) (*Continued*)

Preparation	Comment
Lactate Ringer s (NaCl 0 31 KCl 0 03 CaCl 0 02 and Na lactate 0 31)	Combines efficacy of lactate and three chlorides Use to correct electrolyte imbalance dehydration, acidosis potassium deficiency etc
METABOLITES	
Dextrose (Glucose) 2½% 5% or 10%	For calorigenic requirements (1000 cc 2½% = 100 cal 1000 cc 5% = 200 cal. 1000 cc 10% = 400 cal) To combat acidosis Add insulin 1 unit per gm in diabetic acidosis Use dis tilled water saline Ringer s or lactate as vehicle according to indications above
Water Soluble Vitamins	With dextrose add thiamine 10 to 50 mg riboflavin 5 mg niacinamide 50 mg per liter Add 100 mg ascorbic acid postoperatively with 5 to 10 mg K if there is jaundice bleeding hemorrhagic diathesis or hepatic insufficiency
Alcohol 5% or 10% with Dextro e 5%	Especially in alcoholism but also in non alcoholics for same indications as dextrose alone One liter 5% alco hol with 5% dextrose yields 600 calories One liter 10% alcohol with 5% dextrose yields 1000 calories Addi tional sedative effect in maniacal psychoses· analgesic in painful conditions and soporific Inject slowly with constant observation Do not combine with opiate or barbiturate
Dextran (6%) in physiologic saline	Polysaccharide plasma substitute Use 400 to 3000 cc in forward failure (shock) hypoproteinemia hypoten sion etc Dextran probably metabolized and burned as glucose Not yet commercially available
PROTEIN HYDROLYSATES	
Amigen (Mead) N N.R. with 5% dextrose (Bottles of 125 and 500 cc)	Non antigenic pancreatic hydrolysate of casein (1 3 gm equivalent of 1 gm protein) To maintain nitrogen bal ance correct hypoproteinemia and protect liver give 1000–3000 cc daily
Aminosol (Abbott) with 5% dextrose (Container 1000 cc)	Hydrolysate of beef or pork blood fibrin Contains arginine histidine lysine tryptophane phenylalanine cystine methionine threonine leucine isoleucine valine glutamic acid and 6% ash
Elamine Lyophilized (Interchem) N N R. 60 gm. with diluent	Acid hydrolysate of casein Contains amino acids as above but neither dextrose nor sodium chloride Non pyrogenic with pH range 6 5 to 7 0 Just prior to use restore to volume of 600 cc with diluent
Parenamine (Winthrop) N N R 100 cc vials (15%) 1000 cc flask (6%)	Acid hydrolysate of casein As elamine above but sup plied in 6% solution for injection or 15% solution to be diluted with three parts of diluent.
Protein Hydrolysate (Baxter) 5% N N R. Containers 500 and 1000 cc	Enzymatic digest of ca ein containing amino acids and peptides with or without 5% dextrose

Hypoproteinemia or protein deficiency may result from a decreased dietary intake (famine poverty obstruction of gastro intestinal tract repeated vomiting) *decreased absorption of protein* (diarrhea ulcerative disease of intestine absence of pancreatic juice absence of bile fistulization) decreased formation of blood protein due to disease of liver (*cirrhosis and other forms of hepatic insufficiency*) *increased loss* of protein (albuminuria burns hemorrhage excessive vomiting diarrhea drainage from artificial openings and fistulas) and increased *requirements for protein* (fever pregnancy leukemia and hyperthyroidism)

Hypoproteinemia may result in peripheral edema diminished intestinal motility intestinal distention delayed wound healing diminution of liver function increased susceptibility to infection anemia and increased tendency to thrombosis and embolism

Ordinarily the patient with *hypoproteinemia responds to a mixed high protein diet using 125 to 300 gm of protein daily Concentrates* and hydrolysates should not be employed unless ordinary foodstuffs *cannot be ingested absorbed and digested*

Untoward Reactions The practitioner is cautioned to avoid intravenous infusion of protein hydrolysate if the product can be given orally or by tube feeding since injections may produce untoward effects including nausea vomiting hyperpyrexia vasodilatation abdominal pain convulsions edema and phlebitis or thromboses at the site of injection Cloudy solutions must be discarded and unopened solutions must be stored in a cool place Once opened the solution must be used within the course of a very few hours Infusions must be started at an exceedingly slow rate (30 drops to the minute) and should not *be speeded if it is at all possible and convenient If the patient becomes* restless it is justifiable to give sedatives concurrently

FLUIDS FOR INTRAVENOUS INFUSIONS (p 3775)

Preparation	Comment
DILUENT	
Distilled Water	Substitute for saline in presence of backward failure edema and sodium or chloride intoxication
Sodium Chloride Physiologic Isotonic Solution (0 9%)	Use as vehicle in dehydration especially associated with vomiting and sodium or chloride loss
Ringer s Solution (Isotonic Solution of Three Chlorides)	Contains 0 86% NaCl 0 03% KCl and 0 033 $CaCl_2$ Use as vehicle in dehydration especially with loss of base as in diarrheas fistulas drainage potassium deficiency of diabetic acidosis etc
Sodium Lactate (M/6 Solution)	Contains 1 87 Na lactate Use especially in forward failure (p 920) acidosis and hemo-concentration to increase volume of circulating fluid Calculate that 500 cc for average adult of 150 lbs (70 kg) increases plasma Na 14 millimols per liter corresponding to rise in bicarbonate concentration sufficient to yield 33 volumes CO_2 per 100 cc plasma

tetrachlorethylene are swallowed Two hours later salıne ıs repeated Food is resumed after thorough evacuation Repetition of the anthelmintic is permissible in three weeks if necessary

3 If ascariasis persists despite the use of the above mentioned anthelmintics it may be necessary to give oil of chenopodium (p 1896) The routine for tetrachlorethylene is repeated On the morning of treatment in place of tetrachlorethylene 0 6 to 0 9 cc of oil of chenopodium is washed down with a glass of milk The dose of oil of chenopodium is repeated once or twice at half hour intervals until a total of no less than 1 2 cc and no more than 2 7 cc has been ingested Two hours after the last dose the saline is repeated

4 As a last resort in resistant ascariasis santonin is employed (pp 1896 1898) Three capsules each containing 60 mg of santonin (total 180 mg) are given once daily for two or three consecutive days With each dose a saline laxative is simultaneously administered preferably after breakfast

ASPERGILLOSIS

Principles of Diagnosis and Treatment

1 De pite their wide dissemination in nature A.pergilli infrequently produce clinical manifestations (p 498)

2 The diagnosis of aspergillosis rests on isolation of the fungus from a le ion since there are no pathognomonic clinical manifestations For guidance in therapy the organism must be subcultured and tested against various antibiotics to determine individual sensitivity

3 The few reported infections with aspergilli have been limited to cutaneous inflammations Only with exceeding rarity are manifestations systemic usually predominantly pulmonary (Fig 506 p 2213)

4 Since there is no specific therapeutic agent the clinician who encounters the rare case of systemic aspergillosis is justified in treating the invasion in the manner of actinomycosis (p 4141)

AUREOMYCIN

Aureomycin is a yellow crystalline antibiotic derived from Streptomyces aureofaciens Its wide antibiotic spectrum and virtual absence of toxicity mark its discovery as another epochal contribution to anti infective therapy (p 4219)

Available Products

Aureomycin Hydrochloride N N R (Duomycin Lederle) Capsules 50 and 250 mg Prescribe 25 to 100 mg per kilogram per day (1 75 to 7 gm for average adult weighing 150 pounds)

ASCARIASIS

[Poundworm Infestation]

Principles of Diagnosis and Treatment

Infestations with the roundworm may be limited to invasions of the intestinal tract (ascariasis) or they may involve extra intestinal dis semination throughout the tissues of the body

Extra intestinal invasions are separately considered under the head ings of filariasis (p 4328) and trichinosis (p 4591) The present con cern is *management of intra intestinal infestations* (*Figs* 433 p 1894 and Fig 439 p 1906) which however may penetrate the intestinal barrier and produce evidences of an atypical pneumonitis Hyper sensitivity phenomena in the nature of eosinophilic pneumonitis (*Loeffler s syndrome*) also have been reported

Practical Management

Immediate Care

1 With mixed infestations especially uncinariasis (hookworm) *treat ascariasis first and then proceed to elimination of the smaller worm*

2 Use hexylresorcinol (caprokol crystoids (p 4356) as anthelmintic of choice Order a saline the evening preceding use of the specific The next morning before breakfast give the adult a single dose of 1 gm (5 hard gelatin capsules each containing 0 2 gm) The capsules must be swallowed whole without chewing After five hours repeat the saline Later the patient may resume normal diet

3 Repeat hexylresorcinol after three days if stools have not cleared Supplement oral doses by retention enemas of 200 cc of 1 1000 hexyl resorcinol in warm tap water

4 In regions in which leche de higueron is available as a fresh preparation give a saline cathartic the evening preceding use of the anthelmintic The following morning order a single oral dose of 60 cc of freshly prepared leche in milk Two hours later repeat the saline

Continuing Care (Unfavorable Course)

1 Should hexylresorcinol fail try hetrazan (p 4198) Order about 1 mg per pound of body weight or approximately 140 mg for the average adult weighing 150 pounds Three doses each of three 50 mg tablets are given at 8 hour intervals Two hours after the third dose a saline is administered If stools have not completely cleared repeat hetrazan after ten days

2 With persistent ascariasis despite repeated use of less toxic anthelmintics resort to more toxic preparations Of these *least objectionable* is tetrachlorethylene (p 1895) For a week preceding admin istration of tetrachlorethylene patient is placed on a full diet avoiding fats and alcohol On the night preceding treatment a saline purge is ordered Next morning before food is taken three 1 cc capsules of

Therapeutics

The anti infective capacities of aureomycin and chloramphenicol are so closely parallel that the therapeutic uses of both antibiotics are considered in a single table together with those for terramycin

THERAPEUTICS OF AUREOMYCIN CHLORAMPHENICOL AND TERRAMYCIN

GRAM POSITIVE COCCI

Pneumococci

Despite sensitivity of pneumococcus prefer penicillin unless clinical course suggests a virus pneumonitis In the latter circumstance supplement or substitute aureomycin or chloramphenicol

Staphylococci

Penicillin first choice but supplement with or substitute aureomycin or chloramphenicol if patient is sensitive or organism is penicillin resistant Combine penicillin and aureomycin or chloramphenicol in severe persi tent and recurrent infections Reserve sulfonamide and streptomycins until thorough trial of less toxic antibiotics

Streptococci

Penicillin first choice although most streptococci are sensitive to aureomycin and chloramphenicol Prepare to supplement with or substitute either of latter if patient is sensitive or organi m is resistant Alpha hemolytic streptococci certain strains of beta hemolytic streptococci non hemolytic streptococci group D and Streptococcus fecalis often more sensitive to aureomycin than penicillin Reserve sulfonamide until thorough trial of less toxic antibiotics

GRAM NEGATIVE COCCI

Gonococci

Although organism is somewhat aureomycin sensitive prefer penicillin as preparation of choice

Meningococci

Although meningococci are aureomycin sensitive prefer sulfonamide and penicillin because of greater experience with these preparations Be prepared to supplement with or substitute aureomycin if patient is intolerant of penicillin or sulfonamide or if infection is fulminating and persistent

GRAM POSITIVE BACILLI

B anthrax

Place main reliance on serum with supplementation of penicillin and streptomycin although organism is somewhat sensitive to aureomycin and chloramphenicol Prepare to supplement with or substitute latter if patient is sensitive infection is fulminating or persistent

Co diphtheriae

Organism somewhat aureomycin sensitive Because of greater experience place main reliance on serum and penicillin Prepare to supplement with or substitute aureomycin if patient is sen itive or infection is fulminating or protracted

GRAM NEGATIVE BACILLI

Aerobacter aerogenes

Alcaligenes fecalis

Aureomycin and chloramph nicol first choice Retain streptomycin/sulfonamide as alternatives if patient is sensitive to newer preparations or if organism appears re istant

B fundiliformis

Successful clinical result in a single infection

E coli

Aureomycin first choice with chloramphenicol in urinary and peritoneal infections Combine with streptomycin and/or sulfonamides if organism is re istant or infection is fulminating or protracted

Aureomycin Spersoids (Lederle) Each rounded teaspoon contains 50 mg in chocolate flavored powder Mix with water or milk for palat able drink especially for children One teaspoonful for each 5 pounds of body weight per day approximates 25 mg per kilogram

Aureomycin Hydrochloride N N R (Lederle) Intravenous 50 and 100 mg vials with 10 cc vials of 2 6% leucine or 0 75% sodium car bonate for use as diluent Reserve for use only in gastric intolerance Inject intravenously immediately after preparation of solution Use one fifth calculated oral dose (5 to 20 mg per kilogram or 0 35–1 4 gm daily for average adult weighing 150 pounds)

Aureomycin Hydrochloride Ophthalmic Vials (Lederle) 25 mg with dropper assembly for preparation of borate olution with 5 cc of diluent For local use in milder infections Combine with systemic doses in more serious inva ions

Aureomycin Hydrochloride Ointment (Lederle) (3%) in petrolatum wool fat base

Aureomycin Hydrochloride Troches (Lederle) 15 mg for preven tion and treatment of mixed infections of mucosa of mouth oropharynx and upper respiratory tract

Bacterial Spectrum

The bacterial spectrum of aureomycin covers gram negative cocci gram positive cocci gram negative bacilli gram positive bacilli spiro chetes rickettsia viruses and protozoa It is broader than that of peni cillin or streptomycin in point of fact it exhibits some degree of activity against most organisms that respond to either of these potent anti infective agents Spectrums of chloramphenicol and terramycin parallel that of aureomycin the principal differences being merely quantita tive (p 4243)

Pharmacology

Highest blood levels are obtained two hours after oral doses of aureomycin and detectable levels are maintained for another twelve hours Aureomycin appears in urine one hour after oral doses and excretion continues from six to twelve hours Quantitative recovery of aureomycin is not accomplished in urine so that some is retained by or destroyed in the body Aureomycin is demonstrable in cerebro spinal fluid in therapeutically effective levels in six hour In bile levels are approximately 10 times those of serum Aureomycin tra verses the placental circulation and therefore it is available to the fetus

Aureomycin deteriorates quite rapidly in solution and parenteral injections are painful Hence it is best given by mouth When adminis tered to the human in oral doses of 500 mg (2 capsules) twice daily concentrations in blood reach 0 6 to 2 4 micrograms per milliliter in an hour In urine concentrations of 50 to 80 micrograms per milliliter are observed shortly after detectable blood levels have been attained The urine may turn greenish yellow during excretion of aureomycin

THERAPEUTICS OF AUREOMYCIN CHLORAMPHENICOL AND TERRAMYCIN
(Continued)

RICKETTSIAE *(Continued)*

Reserve PABA for rare instance of organism fastness or fulminating and persistent invasion

VIRUSES

Common Cold
Aureomycin or chloramphenicol merit trial together with antihistamines

Dengue
Despite low morbidity aureomycin and chloramphenicol merit trial

Epidemic keratoconjunctivitis
Aureomycin merits trial by local instillation and oral administration.

Foot and mouth disease
Aureomycin and chloramphenicol merit trial, by analogy

Granuloma inguinale
Aureomycin and chloramphenicol specific. Despite success of streptomycin/sulfonamide more recently introduced antibiotics preferred because of greater ease of administration and lesser toxicity

Herpes zoster
Specific result with chloramphenicol

Inclusion conjunctivitis
Aureomycin specific by local instillation and oral administration.

Infectious mononucleosis
Despite inconsistent results aureomycin and chloramphenicol merit trial

Lymphopathia venereum
Aureomycin and chloramphenicol specific

Measles
Aureomycin and chloramphenicol merit trial

Molluscum contagiosum
Aureomycin and chloramphenicol merit trial

Ornithosis
Aureomycin and chloramphenicol apparently specific

Psittacosis
Aureomycin and chloramphenicol apparently specific

Rabies
Place main reliance on rabies vaccine or hyperimmune serum, but aureomycin and chloramphenicol merit trial or at least, supplementation.

Trachoma
Aureomycin probably specific Use by local instillation and oral administration

Vaccinia, Variola
Successful use in eczema vaccinatum suggests possible efficacy in variola

Virus hepatitis
Aureomycin and chloramphenicol merit trial in conjunction with gamma globulin

Virus pneumonitis
Aureomycin and chloramphenicol apparently specific

AMEBAS AND PROTOZOA

E histolytica (amebiasis)
Unexpectedly favorable clinical report warrants initial trial of aureomycin in combination with non toxic oxyquinolines

Trichomonas hominis
Unexpectedly favorable result in chronic Trichomonas enterocolitis

Giardia
Responds as amebiasis

Surgical Indications

Aureomycin is particularly valuable in surgery of digestive and urinary tracts gallbladder and biliary passages

THERAPEUTICS OF AUREOMYCIN CHLORAMPHENICOL AND TERRAMYCIN
(Continued)

GRAM NEGATIVE BACILLI *(Continued)*

E typhosa
Prefer chloramphenicol to aureomycin Prepare to supplement with latter if infection is fulminating protracted or recurrent

H ducrey (chancroid)
Aureomycin and chloramphenicol first choices despite previous excellent results with more toxic streptomycin and sulfonamide

H influenzae
Despite excellent results in meningitis with combined streptomycin-sulfonamide-antiserum, aureomycin and chloramphenicol are remarkably effective and may be substituted with greater experience particularly if patient shows sensitivity to more toxic antibiotics and antiserum

H Koch Weeks
Specific responses to local instillations of aureomycin

H pertussis
Aureomycin first choice with chloramphenicol Combine with streptomycin, if needed Polymyxin and aerosporin also efficacious but much more toxic

Kl pneumoniae (Friedlander)
Aureomycin first choice with chloramphenicol Retain streptomycin-sulfonamide as alternatives if patient is sensitive to newer preparations or infection is fulminating or persistent

M mallei (glanders)
Aureomycin and chloramphenicol merit trial

M melitensis (brucellosis)
Aureomycin first choice with chloramphenicol, Keep streptomycin-sulfonamide for alternative if infection is persistent or fulminating In acute brucellosis give 2 4 to 3 gm orally for at least two weeks

M tuberculosis
Of no value in the treatment of tuberculosis despite test tube sensitivity of many organisms (E R Long)

P pestis (plague)
Despite excellent results with streptomycin-sulfonamide aureomycin and chloramphenicol may replace more toxic antibiotic when greater experience has been obtained

P tularensis (tularemia)
Aureomycin first choice Reserve chloramphenicol if patient shows sensitivity or organism is resistant

Salmonellae (paratyphoid)
Prefer chloramphenicol as in typhoid fever

Shigellae (bacillary dysentery)
Prefer chloramphenicol to aureomycin as in typhoid fever Reserve sulfonamide for supplementation or substitution if necessary

Vibrio comma (cholera)
Organism sensitive to aureomycin and chloramphenicol With greater experience either or both may replace potentially more toxic sulfonamide

D Morax Axenfeld
Response to local instillation with aureomycin

TREPONEMES (spirochetes borrelia leptospira)
Despite moderate efficacy in syphilis (Tr pallidum) and relapsing fever (Bo recurrentis) retain penicillin and arsenic as preparations of choice Consider aureomycin in rare instance of patient sensitivity to penicillin or arsenic and in treatment of serum fast Local applications and troches merit trial in fusospirochetosis (Vincent s infection)

RICKETTSIAE
Aureomycin and chloramphenicol unqualified preparations of choice Use either or both, depending on patient sensitivity and organism resistance

tated patients with chronic disease must be ambulated as soon as is possible

Combined Antibiotic Therapy

Combined antibiotic therapy using aureomycin or chloramphenicol with penicillin permits the clinician to employ anti infective therapy for prophylaxis or cure with broadest coverage of the bacterial spec trum and almost minimum risk of toxicity

Exemplifying this in a program of venereal prophylaxis ingestion of 2 tablets each of 250 000 units of penicillin together with 4 capsules of aureomycin taken within a few hours after exposure may provide effectual prophylaxis against gonorrhea chancroid granuloma ingui nale lymphopathia venereum and syphilis

Illustrative of curative potentialities of combined antibiotic therapy the practitioner confronted with a pneumonitis may observe a lysis of temperature and detoxification whether the patient is suffering from pneumococcal or viral pulmonary infection

Aureomycin Versus Chloramphenicol and Terramycin

The choice between aureomycin and chloramphenicol involves hair splitting If there is any doubt as to which to prescribe it is suggested that each product be ordered in half strength in the manner that has proven so satisfactory with sulfonamide derivatives Terramycin appears equally effective and somewhat less expensive

BACILLOMYCIN

An antibiotic derived from B subtilis Bacillomycin lacks antibacterial action but attacks many pathogenic fungi

Available Products

Bacillomycin is not yet commercially available

Therapeutics

Experimentally bacillomycin has been used in the treatment of histo pla mosis Intramuscular injections of 50 mg given every six hours however caused local pain and slough with temperatures as high as 104 F

BACITRACIN

An antibiotic prepared from cultures of B subtilis Systemic adminis tration of bacitracin is not advised since the preparation is nephrotoxic when given parenterally

In surgery of the bowel oral doses (approximating 500 mg daily) reduce pathogenic bacteria of the intestinal tract more rapidly and seemingly as efficiently as insoluble sulfonamide while permitting resection of small and large bowel lesions with greater safety (Strax and Wright 1949) As a result the over all mortality of acute peritonitis is reduced by one half as compared with a series treated with penicillin sulfadiazine and streptomycin Equally encouraging results are reported by these same authors in idiopathic ulcerative colitis regional ileitis post cholecystectomy syndrome and urinary tract infections In the last named as a matter of fact Strax and Wright regard aureomycin as the drug of choice

High concentrations of aureomycin in bile make the new antibiotic particularly valuable in procedures involving gallbladder and biliary tract

In Radiation Therapy

For reasons not yet completely clear aureomycin protects against irradiation sickness whether the physical modality is given therapeutically (as in x ray treatment of malignancy) or through exposure to products of atomic fission

If preliminary observations are confirmed aureomycin increases the tolerance of patients to x ray therapy and may prove of inestimable indirect value in the treatment of cancer

Toxicology

Aureomycin has no significant toxicology Many patients however develop nuisance symptoms including nausea vomiting diarrhea and anorectal burning An occasional instance of angioneurotic edema has been reported (J A M A 143 653 1950)

Gastric tolerance is increased by simultaneous administration of large quantities of water milk or cream cheese Aluminum salts suggested in early experiments are best omitted since they tend to reduce blood concentrations of antibiotic (J A M A 141 938 1949) If gastrointestinal disturbances are annoying or persistent aureomycin may be injected intravenously or chloramphenicol substituted in somewhat larger doses

Antitherapeutic Devices (p 4133)

An occasional patient exhibits allergy to aureomycin just as occurs with every other antigen In consequence it is wise to give antihistamine concurrently with the antibiotic particularly to patients with a known history of allergic hypersensitivity

Thus far bacterial resistance and fastness have not been noted nor have more serious tuberculin type hypersensitivity phenomena been observed

The single important anti therapeutic threat posed by aureomycin appears to be its effect in increasing blood coagulability Significant changes are noted shortly after administration of therapeutic doses raising the hazard of complicating thrombophlebitis and secondary embolic phenomena Aureomycin treated post operatives and debili

tated patients with chronic disease must be ambulated as soon as is possible

Combined Antibiotic Therapy

Combined antibiotic therapy using aureomycin or chloramphenicol with penicillin permits the clinician to employ anti infective therapy for prophylaxis or cure with broadest coverage of the bacterial spec trum and almost minimum risk of toxicity

Exemplifying this in a program of venereal prophylaxis ingestion of 2 tablets each of 250 000 units of penicillin together with 4 capsules of aureomycin taken within a few hours after exposure may provide effectual prophylaxis against gonorrhea chancroid granuloma ingui nale lymphopathia venereum and syphilis

Illustrative of curative potentialities of combined antibiotic therapy the practitioner confronted with a pneumonitis may observe a lysis of temperature and detoxification whether the patient is suffering from pneumococcal or viral pulmonary infection

Aureomycin Versus Chloramphenicol and Terramycin

The choice between aureomycin and chloramphenicol involves hair splitting If there is any doubt as to which to prescribe it is suggested that each product be ordered in half strength in the manner that has proven so satisfactory with sulfonamide derivatives Terramycin appears equally effective and somewhat less expensive

BACILLOMYCIN

An antibiotic derived from B subtilis Bacillomycin lacks antibacterial action but attacks many pathogenic fungi

Available Products

Bacillomycin is not yet commercially available

Therapeutics

Experimentally bacillomycin has been used in the treatment of histo plasmosis Intramuscular injections of 50 mg given every six hours however caused local pain and slough with temperatures as high as 104° F

BACITRACIN

An antibiotic prepared from cultures of B subtilis Systemic adminis tration of bacitracin is not advised since the preparation is nephrotoxic when given parenterally

Available Products

Bacitracin Ointment (C S C or Upjohn) One gram = 500 units

Bacitracin Ophthalmic Ointment (C S C or Upjohn) One gram = 500 units

Bacitracin Powder (C S C or Upjohn) Sterile vials containing 2000 10 000 or 50 000 units The powder remains stable for eighteen month Add sterile distilled water to make a solution of 500 to 1000 units per cc Keep freshly prepared solution in refrigerator where it remains stable for eighteen months

Bacidrin (Upjohn) A lyophilized nasal preparation Add 15 cc of water to make a solution of which 1 cc contains 200 units of bacitracin and 5 mg of ephedrine Store in ice Instill or spray intranasally every two hours

Bacterial Spectrum

Bacitracin has a profound antibacterial effect paralleling penicillin It is effective against staphylococci streptococci gonococci *V comma* of cholera P pestis of plague M melitensis of brucellosis and other gram negative and gram positive pathogens It also exhibits some activity against E histolytica treponemes and fungi Its local effectiveness is not inhibited by admixture with plasma blood pus tissue juices or penicillinase It does not produce cross sensitivity with penicillin and may be used locally in place of penicillin to avoid sensitization phenomena

COMPARATIVE TOPICAL EFFECTS OF BACITRACIN AND PENICILLIN

	Bacitracin	Penicillin
Inactivated by bacterial penicillinase	No	Yes
Inactivated by exudate	No	Yes
Inactivated by tissue fluid	No	Yes
Inactivated by leukocytes	*No*	Yes
Sensitization	Approximately 1%	In excess of 10%
Later sensitization to parenteral injection of penicillin	No	Yes
Parenteral use	I ot advised	Highly recommended
Toxicity (Parenteral)	Renal	Negligible

Therapeutics

Bacitracin may be used as ointment collyrium wash aerosol spray instillation or local infiltration For the last purpose injections are made with 0 1 to 5 cc of a solution containing 400 units to the cc together with 2% procaine

For local or topical use the site is first cleansed with warm saline solution to remove all crusts Bacitracin wash or ointment is then applied in conditions such as localized pyoderms infected wounds carbuncles furuncules impetigo hordeolum abscesses ulcers ecthyma folliculitis cellulitis and sinus tracts The collyrium may be instilled locally in the treatment of conjunctivitis keratitis and other superficial ocular infections

Oral bacitracin is under trial in amebiasis and the treatment of other enteric infections such as cholera plague etc The efficacy of less toxic aureomycin and chloramphenicol makes it appear unlikely that bacitracin will be widely employed in these conditions

BACTERIAL ALLERGIC HYPERSENSITIVITY

With increasing recognition of the etiologic role of bacteria in the production of allergic hypersensitivity reactions particularly of the chronic tuberculin type variety (p 4169) it becomes imperative to eliminate offending micro-organisms in order to palliate prevent and/or avoid serious and at times fatal clinical accidents (p 552)

Of available general therapeutic principles the practitioner employs mechanical measures especially surgical drainage and extirpation of foci (p 42) anti infective agents particularly hypoallergenic antibiotics (p 4179) desensitization or hyposensitization employing bacterial vaccines (p 4180) and prophylaxis or palliation with antihistamines and adrenergens (p 4210)

General Principles of Diagnosis and Treatment

1 Attempt elimination of offending bacteria by use of *antibiotics* Avoid sulfonamide which may produce tuberculin type sensitization

2 If bacterial infection cannot be eliminated by antibiotic treatment consider *surgery* where indicated as in chronic infection of nasal accessory sinuses or where there is inadequate drainage due to a deviated nasal septum or an hypertrophied turbinate causing nonseasonal vasomotor rhinitis (p 2098) particularly insist on drainage of sphenoid sinuses in uveitis (p 1632)

3 Concurrently with antibiotic administer antihistamine Continue use of histamine antagonist for a prolonged period of time i e at least two weeks after last dose of antibiotic

4 Use prophylactic antibiotic therapy (p 4362) at stated intervals to prevent reinfection by offending organism (as in rheumatic fever p 4493)

5 Consider desensitization with bacterial vaccine in infections resistant to antibiotics (deep fungus disease such as blastomycosis etc)

BACTERICIDES

Prior to introduction of sulfonamide the effective bactericides were salts of metals These possessed potent test tube activity and more than considerable host toxicity By present standards compounds of mercury arsenic antimony gold silver and bismuth are relatively feeble but formidably dangerous anti infective agents

With birth of the Golden Age of Therapeutics an entirely new concept of bactericidal and bacteriostatic activity came into being To be sure sulfonamides evinced some host toxicity but even this appeared negligible compared to potential untoward reactions to antimony arsenic gold and mercury Since introduction of penicillin the streptomycins chloramphenicol and aureomycin the toxicity of sulfonamides appears almost as formidable as that of older metallic salts

So rich is the modern antibacterial artillery that the physician often is uncertain which potent agent to use and whether to employ a single preparation or blanket the field by combining two or even three antibiotics as in Probatory or Desperation Therapy (p 4221) The chart which follows indicates in broad terms the opulence of the field of anti infectives

SPECTRUM OF ANTIBACTERIAL AGENTS

Anti infective *Agents*	Gram negative Cocci	Gram positive Cocci	Gram negative *Bacilli*	Gram positive *Bacilli*
Aureomycin	+	+	+	+
Chloramphenicol	+	+	+	+
Dihydrostreptomycin	0	+	+	0
Neomycin	0	+	+	0
Penicillin	+	+	0	+
Streptomycins	+	+	+	0
Sulfonamide	+	+	+	0
Sulfones	0	0	+	0

BACTERIOIDES FUNDULIFORMIS INFECTION

General Principles of Diagnosis and Therapy

1 Bacterioides a large group of gram negative anaerobic non sporulent bacteria are normal inhabitants of mucous surfaces rupture of which may produce bacteremia

2 In the test tube bacterioides are insensitive to penicillin streptomycin and sulfadiazine but not to aureomycin

3 In a report of two recent cases recovery followed treatment with aureomycin in doses of 750 mg on the first day 2 gm on the second day 4 gm on the third day and 5 gm daily thereafter until all manifestations of infection had been dissipated Four patients previously treated with chemotherapy other antibiotics and supportive therapy died

BACTERIOP GE

Bacterioph ges (d Herelle) are in actuality viruses which invade bacteria Th possess the following characteristics They are capable of producin n l is of bacterial cells Duri s of

infected bacteria bacteriophages multiply They can be propagated indefinitely through series of cultures Bacteriophages are sufficiently small to pass through filters which hold back bacteria they are not sedimented in ordinary centrifuges

Bacteriophages are specific capable of lysing bacteria of one genus they do not ordinarily act on bacteria of another

Therapeutics

Bacteriophages have never been sufficiently perfected for general use by the practitioner They pose the threat of introducing living virus to combat invasion of host tissues by another living microbe

Effective bacteriophages have been developed against P pestis (plague) V comma (cholera) and staphylococci Inasmuch as each of these diseases responds to more easily available antibiotic whose intro duction into the human body is simpler and safer specific bacterio phages mu t be regarded as obsolete

BAL

[British Anti Lewisite]

BAL (2 3 dimercaptopropanol) was prepared originally as a decon taminant for use in blister gas attacks In peacetime medical prac tice it has proven a most effective antidote in poisonings due to arsenic gold antimony mercury cadmium bismuth vanadium chromium zinc nickel and lead (p 762)

Available Products

Solution BAL in Oil (Hynson) Ampuls containing 4 5 cc of 10% BAL and 20% benzyl benzoate in peanut oil

Pharmacology

BAL is a dithiol As such it competes with physiologically essential cellular SH groups for arsenic mercury and gold In this way it pre vents combination of heavy metal with these groups The stable com bination of BAL and heavy metal is rapidly excreted ridding the body quickly of toxic agent

In mercurial poisoning the action of BAL is less effective due to the fact that excretion of mercury causes rapid and extensive renal damage which cannot be corrected through administration of antidote

Therapeutics

In arsenic and gold poisonings where BAL is most effective the antidote is injected intramuscularly in an initial dose of 3 mg per kg of body weight (approximately 2 cc of 10% solution in oil for an adult weighing 150 lbs) The do e is repeated every four hours for two days every six hours on the third day and every twelve hours thereafter for

ten days or until complete recovery has taken place provided that untoward manifestations due to BAL have not previously been encountered

In mercury lead antimony and bismuth poisonings results have been less conclusive and larger doses are required For initial deposit 5 mg per kg of body weight are recommended (3 5 cc of 10% solution in oil for the adult weighing 150 lbs) This dose is repeated at the end of one two and ten hours Thereafter 2 to 2 5 cc are injected each twelve to twenty four hours depending on the clinical course and the presence or absence of toxic manifestations due to the antidote itself

BAL is particularly useful in the treatment of arsenical dermatitis hemorrhagic encephalopathy agranulocytosis and toxic hepatitis Had BAL been available in the pre penicillin era arsenotherapy of syphilis and allied treponematoses might have been considerably less hazardous and significantly more efficacious Currently the survival of arsenotherapy may be decided by the extent to which penicillin results can be bettered by combined use of metal and antibiotic and the extent to which BAL mitigates arsenic toxicity

Toxicology

BAL is itself a poison Large doses approximating the concentrations given in mercurial poisoning may produce nausea vomiting headache *burning of lips mouth throat and eyes generalized muscular* aches burning and tingling of the extremities peripheral circulatory collapse a sense of constriction in the chest and anxiety These occur within fifteen to twenty minutes after injection and may be prevented or ameliorated by preliminary use of 25 mg of ephedrine given orally a half hour before injection and repeated at thirty to ninety minute intervals if necessary

BALANTIDIASIS

Principles of Diagnosis and Treatment

1 The presence of Balantidia in the stool is not necessarily indicative of the pathogenicity of the organism (Fig 423 p *1892) Only if* there is no other obvious cause for symptoms should the organism be regarded as the etiologic agent (p 1893)

2 Since enterocolitis due to Balantidia is a relatively benign and self limited disorder use of therapeutic agents which have a capacity for toxicity is not warranted Preference is given to relatively non toxic amebacides employed in intra intestinal infestations

Practical Management

Immediate Care

1 Order 2 tablets of diodoquin each of 210 mg five times daily for ten days

2 If symptoms are not controlled *and/or stools remain positive fol*

lowing the first course repeat after an interval of a week to ten days Other oxyquinolines (p 4442) such as vioform and chiniofon are less effective and may complicate the clinical picture by producing diarrhea medicamentosa on the second or third treatment day

3 Of more drastic remedies tried in balantidiasis emetine oil of chenopodium and tryparsamide appear excessively toxic for use in a benign disease If oxyquinolines fail aureomycin or pentavalent arsenicals (carbarsone) may be substituted as in amebiasis (p 4183)

4 For persistent symptoms intramuscular injections of 2 7 mg of biniodide of mercury have been suggested After the first injection nine reported patients became symptom free they were parasite-free after the second injection

BARBITURATE POISONING ACUTE

General Principles of Diagnosis and Therapy

1 Although the incidence of acute barbiturate poisoning has increased alarmingly most patients take considerably less than a lethal dose Consequently profoundly poisoned or fatal instances as seen in institutional practice are rarely encountered in private practice More often than not the suicidal attempt is a gesture that does not require inauguration of heroic measures later described

2 If the dose of the barbiturate appears to have been less than 50 grains a favorable prognosis is warranted and the therapeutic policy may be one of watchful waiting amounts in excess of 100 grains approach the lethal quantity intermediate doses may or may not be fatal depending on individual circumstances and efficacy of therapy

3 The paramount danger in barbiturate poisoning is respiratory depression and not loss of consciousness So long as the color is satisfactory and cardiorespiratory activities are maintained there is no immediate danger

4 The earlier the patient is seen the better the prognosis if swallowed drug can be removed partially by gastric lavage or induced emesis

5 The longer the patient survives following ingestion of drug the better the prognosis particularly if a rapidly acting barbiturate has been taken

6 In the use of analeptic (p 4188) for the seriously poisoned individual the fear of producing convulsions has been exaggerated In point of fact induced convulsions may be regarded as shock therapy

Practical Management

Immediate Care

1 If the patient is still conscious on arrival or can be aroused induce vomiting by home remedies such as mustard in water or ipecac or give an injection of 5 mg of apomorphine

2 If the patient is asleep on arrival but respirations are not excessively depressed intubate the stomach intranasally and lavage with warm water or tea Retain lavage washings for chemical analysis and for medicolegal purposes

3 If the patient is deeply somnolent with evidence of marked cardiorespiratory depression prepare to inject analeptic For immediate effect prefer metrazol Introduce intravenously 3 cc of 10% solution Observe effects carefully Grimacing twitching or return of consciousness suggest that the poisoning is not excessively severe Failure of response requires repetition of the dose and consideration of supplementation with picrotoxin later described

4 If metrazol is not available for rapid effect prefer amphetamine sulfate as second choice Inject intravenously 10 to 40 mg Prepare to interrupt injection on appearance of sympathomimetic side effects such as tachycardia elevation of blood pressure etc

5 Despite enthusiastic reports reserve nikethamide (coramine) for third choice as a rapidly acting analeptic If metrazol or amphetamine cannot be obtained inject intravenously 3 cc (750 mg) of nikethamide

6 If the rapidly acting analeptics are successful and consciousness returns it may not be necessary to use picrotoxin However if there is failure of response to metrazol amphetamine or nikethamide or if rapidly acting analeptics produce only a brief return of consciousness followed by somnolence inject intravenously an initial dose of 2 cc of 0 3% solution of picrotoxin

7 Since the maximum effect of picrotoxin does not occur for approximately thirty minutes repetition of the longer acting analeptic must be postponed Meantime if respiratory depression is profound repeat the rapidly acting analeptic using 3 to 5 cc of metrazol 20 to 40 mg of amphetamine or 3 cc of nikethamide

8 If respirations are not effectively restored thirty minutes after the first picrotoxin injection repeat the analeptic increasing the dose to 3 cc (9 mg) Successive doses given at 30 minute intervals may be increased if necessary to 5 cc (15 mg)

9 Since the effective picrotoxin dose for medullary stimulation approximates the convulsive dose the patient may develop seizures These need not cause alarm unless they are too frequent or too violent Under either of the latter circumstances it may be necessary to use intravenous injections of a rapidly acting barbiturate such as sodium pentothal in sufficient amount to produce quiet

10 Just as soon as respirations have been re established pass an endotracheal tube to clear the airway and permit suction removal of bronchial mucus or of gastric lavage washings that may have spilled over into the respiratory passages

[illegible] artificial respiration manually or instrumentally pro-

[illegible] herapy by mask or tent

[illegible] dy warmth with warm blankets

Order 2 table [illegible] 000 units of procaine penicillin G in oil with 2%

[illegible] earate to prevent hypostatic or aspiration pneu

[illegible] days [illegible]

14 Catheterize bladder and repeat every six or eight hours Keep urine for medicolegal examination

15 As soon as circumstances permit, set up an intravenous drip using 5% dextrose in phy iologic saline for the first 2 000 cc Use the rubber tubing for injection of analeptic if required

16 As soon as consciousness returns urge the patient to take fluids orally Maintain vigilance to prevent further attempts at suicide

17 Each twenty four hours repeat deposit of penicillin

18 Remember that there is no substitute for eternal vigilance in the treatment of barbiturate poisoning The physician must be in constant attendance He must be prepared to shift the therapeutic program according to patient responses So long as cardiorespiratory activities are maintained recovery is possible With beginning failure of either system larger doses of analeptic are required since the fear of inducing convulsions does not compare to the hazard of anoxemia

19 Try to have a consultant psychiatrist see the patient during the acute episode At this time much important material may be obtained and formal psychotherapy may be inaugurated

BISMUTH

Except as an accessory to penicillin in the treatment of syphilis the therapeutic usefulness of parenterally administered bismuth preparations (p 126) appears very limited

For systemic effect the practitioner has the choice of aqueous solutions solutions in organic solvents oily solutions suspensions in oil or water oral tablets and of a product combining bismuth and arsphenamine (bismarsen) Of these bismuth subsalicylate in oil U S.P (10%) is least objectionable It may be deposited intramuscularly once weekly in a dose of 1 cc equivalent to 100 mg of metal

Available Products

Suspension Bismuth Subsalicylate in Oil with 3% Chlorobutanol (Abbott Endo Parke Davis Smith Dorsey Upjohn)

Toxicity

See p 127

Antidote

BAL (p 4251)

BLASTOMYCOSIS

[Gilchrist s Disease Lutz Splendore Almeida s Disease Paracoccidioidal Granuloma Cryptococcosis Busse Buschke s Disease]

Principles of Diagnosis and Treatment

1 Blastomyces (Fig 75 p 486) are capable of producing cutaneous lesions (Fig 966 p 3311) readily diagnosed by simple laboratory tech

nics *Systemic blastomycosis is less frequently recognized It requires* serious consideration in the management of idiopathic chronic osteo myelitis (Fig 78 p 494) and chronic pneumonitis (Fig 503 p 2211) when the usual pathogens cannot be demonstrated after careful and repeated searches

2 To assist in the definitive diagnosis of blastomycosis the prac titioner has recourse to sputum cultures on special media a cutaneous reaction and a complement fixation test Of these only the first is com pletely satisfactory skin tests may produce false negative responses particularly in terminal infections the complement fixation reaction while it does not give false positive tests gives an occasional false nega tive when sputum examinations are definitely positive

3 The treatment of systemic blastomycosis is most unsatisfactory With the exception of reports of successful use of penicillin in a single patient there appears to be no subject on which authorities agree except that none of the alleged specifics produces consistently favor able responses Reported results of iodide therapy best illustrate the confusion that exists Thus it is stated that in the treatment of systemic types of blastomycosis it is believed that iodides not only fail to arrest the disease but may cause a rapid spread of lesions On the other hand claims are made that after desensitization with vaccine iodides can be more safely administered and sometimes may cure the infection Starrs and Klotz (*whose cla sical article is recommended to those specially interested in blastomycosis*) state that iodides usually have no effect and again that *in some cases iodides do actual harm* (Arch Int Med 82 1 1948)

4 Under these circumstances with disagreement or unsatisfactory reports of therapy from all authorities the practitioner who treats an occasional patient suffering from systemic blastomycosis is justified in pursuing Probatory and Desperation Anti infective Therapy If possible subcultures of the fungus are obtained for test tube estimation of its sensitivity to the various antibiotics presently available

Practical Management

Immediate Care

1 If cutaneous lesions of blastomycosis can be excised without excessive scarring or disfigurement surgical excision is warranted in view of the gravity of the disease and the unsatisfactory status of therapy Those lesions which cannot be excised may be incised and thoroughly curetted or cauterized under general anesthesia

2 Extensive cutaneous lesions not surgically accessible may be exposed to roentgen therapy which has considerable potential for benefit and very little hazard of toxicity

3 *For systemic management follow steps recommended* in the treat ment of actinomycosis (p 4141) with the exceptions noted below

4 Obtain blastomycosis vaccine from Dr Donald S Martin of the Duke University School of Medicine Durham North Carolina With

this vaccine make an intracutaneous test using 1 1000 dilution A punctate erythema appearing about the site of injection within fifteen to twenty minutes indicates sensitivity

5 Desensitize positive reactors by subcutaneous injections of 0 1 cc of vaccine using the dilution which produces minimum erythema Increase each dose by increments of 0 1 cc every second or third day if po sible until a full dose of 1 cc of undiluted vaccine can be administered

6 Do not inaugurate iodide therapy until positive reactors have been desensitized Vaccine therapy however may be given immediately to non reactors

7 Iodides may be given orally intravenously or by inhalation For oral u e order saturated solution of potassium iodide in a dose of 0 3 cc three times daily in water soup or milk Increase the dose daily by increments of 0 1 cc until 4 cc are given three times daily Stop iodide administration when manifestations of iodism (p 612) appear

For iodide inhalation obtain a special inhalor of the types manufac tured by Warren Collins or Burnham Start inhalations with 0 2 cc of ethyl iodide three times daily Increase each dose by increments of 0 1 cc until a full dose of 1 cc can be tolerated three times daily

For intravenous injections of iodide sodium salt is usually employed though it is not clear why a simple salt should be given intravenously when it is so readily absorbed by mouth or inhalation

8 During iodide therapy be on the alert for chronic tuberculin hypersensitivity manifestations (p 4169) possibly caused by the intended therapeutic agent

Continuing Care (Favorable Cour_e) (Unfavorable Cour_e) (Pro gressively Unfavorable Course) See Actinomycosis

BLOOD AND SERUM

Blood functions as a potent anti infective agent Injections of homo logous and heterologous blood and/or their fractions or components are used to produce artificially acquired active and passive immunity

Homologous Human Blood

Homologous human blood is used particularly to increa e the resist ance of depleted and anemic patients In addition derivatives and frac tions are injected for specific anti infective therapy as exemplified by convale cent serums and gamma globulin

Homologous products are employed primarily for prophylaxis since they have a low antibody titer They are of no value as antitoxic agents but pos ess some antibacterial potential as exemplified particularly in pertussis They enjoy the advantage over heterologous products in that they do not produce allergic hypersensitivity reactions

Heterologous Antibacterial and Antitoxic Serums

Heterologous bloods their component fractions and derivatives usually are drawn from horses unless otherwise stated They are employed for passive transfer of preformed antibody specifically pro duced by injection of offending antigen into experimental animals

In contrast to homologous human blood heterologous serums usually are of high antibody titer but their introduction may result in serious and at times fatal hypersensitivity reactions (p 4187)

The use of both homologous and heterologous bloods and serums has diminished since introduction of antibiotics The newly available anti infective agents are simple to administer relatively non toxic power fully bacteriostatic and bactericidal and rarely productive of significant hypersensitivity reactions

It is only for antitoxic effects that heterologous serums excel such products as penicillin aureomycin and chloramphenicol In the treat ment of invasions caused by organisms capable of secreting soluble toxin (diphtheria gas gangrene tetanus botulism and certain strep tococci) serum therapy continues to be of prime importance with antibiotic used as supplementation

By contrast to antitoxins antibacterial serums approach obsolescence except perhaps in the treatment of plague pertussis rabies and *H influenzae meningitis*

HOMOLOGOUS BLOOD AND DERIVATIVES

Whole Citrated Normal Blood

Obtain from Wassermann negative healthy donor by phlebotomy (p 3780) After cross matching transfuse (p 3711 and 3778) to raise general immunity

Whole Citrated Normal Banked Human Blood

Obtain from blood bank (p 3778) Irradiate to prevent homologous serum hepatitis (p 4358) Cross match and transfuse as above

Whole Citrated Convalescent Human Blood

Obtained from donor recently convalescent from specific disease or actively immunized against invading micro-organism

Normal Human Serum U S P

(Deutsch Hyland)

Rarely of significant antibody titer Prefer globulin fractions when available Irradiate to prevent homologous serum hepatitis (p 4358)

Citrated Normal Plasma U S P

(p 3778)

Prefer Irradiated Lyovac prepared from fresh citrated human blood, taken from healthy donors pooled, flash frozen dehydrated under high vacuum by lyophile process and sealed Requires neither typing nor cross matching One unit equals two units of whole blood Available in 50 250 and 500 cc vials Use principally to restore circulating protein, supply complement and combat shock Antibody titer rarely significant Do not use in nephrosis because of high sodium content and because only half of protein is albumin fraction, most needed by the patient.

Albumin Fraction N F

(Cutter)

Salt poor fractionate of pooled human plasma Supplied in vials containing 5 gm with 20 cc of buffered diluent. Has no value as anti infective agent but is useful in hypoproteinemia, forward failure or shock, or nephrosis Inject 1 cc per pound of body weight, per day intravenously

HOMOLOGOUS BLOOD AND DERIVATIVES (*Continued*)

Human Serum Immune Gamma Globulin Fraction U S P
(Cutter Wyeth Lederle)
Contains concentrated antibody factors for passive immunization of certain communicable diseases especially measles mumps pertussis and virus hepatitis Each 2 cc is the equivalent of 40 cc of original plasma Give 0 1 cc per pound of body weight intramuscularly for prophylaxis of measles give 0 22 cc per pound of body weight for modification of measles if patient is first seen on fourth to seventh day after exposure
To prevent or modify virus hepatitis inject 10 cc in pre-icteric phase if possible
To prevent mumps complications give 40 to 60 cc intramuscularly if available
For prevention or treatment of pertussis give 2 5 cc intramuscularly preferably of a serum especially prepared from healthy hyperimmunized human donors (Cutter) Repeat after twenty four or forty-eight hours if necessary

Human Immune Globulin U S P Placental Extract
(Lederle Sharp & Dohme Wyeth)
For prevention of measles give 2 to 10 cc by intramuscular injection if human serum gamma globulin fraction is not available For modification inject intramuscularly 2 to 5 cc if patient is first seen four to seven days after exposure Repeat after twenty four to forty-eight hours if possible

Human Fibrinogen
(Cutter)
Contains 60% fibrinogen and 40% globulins including antihemophilic fraction. Prefer antihemophilic globulin (see below) for hemophilia (p 1118)

Fibrin Foam and Thrombin
(Cutter)
Available in segments of 250 mg Moisten with thrombin solution for use as absorbable hemostatic in general surgery dentistry and neurosurgery

Thrombin Coagulum
Powder for use with fibrin foam as hemostatic Prefer combined fibrin foam with thrombin (see above)

Fibrin Film
(Cutter)
Available in sterile sheets for use as a protective particularly in treatment of denuded areas as in burns and neurosurgery

Antihemophilic Globulin
(Cutter)
Globulin fraction containing fibrinogen Intravenous dose of 5 cc reduces clotting time to less than ten minutes within half hour Effect persists for four hours Of tremendous value as hemostatic in hemophilia as prophylactic when surgery becomes necessary in these patients (p 1118)

Resuspended Red Cells
Obtained after removal of plasma May be re infused in treatment of anemias (p 1055)

Modified Globulin
Protein component of hemoglobin after splitting off iron containing pyrrole group Residual protein (globin) modified to make concentrated preparation of low viscosity Delivers triple dose of protein per unit as compared with plasma Not yet commercially available

Prothrombin
Impure product consisting largely of beta-globulin Not commercially available

Human Measles Immune Serum N F
(Milwaukee and Deutsch Serum Centers)
Prefer gamma globulin when available For prevention or modification of measles inject intramuscularly 10 to 20 cc

Human Scarlet Fever Immune Serum N F
(Milwaukee and Deutsch Serum Centers)
For prevention, inject intramuscularly 10-20 cc For active treatment prefer penicillin and aureomycin.

HOMOLOGOUS BLOOD AND DERIVATIVES (*Continued*)

Human Pertussis Immune Serum N F
(Hyland *Philadelphia Serum Exchange*)
Lyophilized or concentrated globulin fraction For prophylaxis inject 20 cc intramuscularly every day or every second day for three injections For treat ment of very sick children, inject 60 to 100 cc intravenously diluted to 300 cc with sterile physiologic saline May be superseded by aureomycin or chlor amphenicol

Human Rubella (German Measles) Serum
Not commercially available Obtain from recent convalescents for use in early months of pregnancy to prevent congenital disorders of infancy (p 4509)

Human Poliomyelitis Immune Serum
(Hyland)
Desperation measure for use in prophylaxis of infantile paralysis during an epidemic Inject 10 to 20 cc intramuscularly Repeat daily or every second day for two or three injections if material is available

Human Plague Immune Serum
Unofficial but recommended by experts for prevention of plague Inject 10 to 20 cc intramuscularly Repeat after twenty four to forty eight hours if material is available

Human Tularemia Immune Serum
Unofficial Superseded by aureomycin and chloramphenicol

Human Rocky Mountain Spotted Fever Immune Serum
Unofficial Not commercially available Superseded by aureomycin and chloramphenicol

Human Yellow Fever Immune Serum
Unofficial but recommended by experts in treatment of yellow fever

Human Epidemic Parotitis (Mumps) Immune Serum
Unofficial Not commercially available Obtain from recent convalescents for treatment of adults to prevent orchitis and oophoritis Inject 10 to 20 cc intra muscularly Repeat twice if material is available

Human Brucellosis Immune Serum
Unofficial Superseded by aureomycin and chloramphenicol

Human Bacillary Dysentery Immune Serum
(Anti Shigellosis)
Unofficial Superseded by chloramphenicol and sulfonamides

Human Spirochetal Jaundice Immune Serum
Unofficial Superseded by penicillin and perhaps aureomycin

Human Typhus Immune Serum
Unofficial Superseded by aureomycin and chloramphenicol

HETEROLOGOUS SERUMS AS ANTI INFECTIVE AGENTS

WARNING Injection of Heterologous Serum may cause fatal *anaphylactic shock* or *serum sicknes* For prevention treatment detection of hyper ensitivity and methods for desensitization, see p 4191

Antivenin (Crotalus) N N R
(Wyeth)
Specific for snake bite (rattle nake water snake moccasin, etc) (p 3196) Inject 15 to 75 cc intramuscularly or intravenously with equal amount in the vicinity of bite (p 4523)

Antivenin (Latrodectus Mactans) N N R
(Lyovac Sharp & Dohme)
Specific for black widow spider bite Inject 2 5 cc intramu cularly Repeat frequently if necessary (p 4229)

Botulism Antitoxin N N.R.
(Lederle)
Desperation remedy in botulism. Inject 2500 units subcutaneously for prophylaxis and 10 000 units intravenously for treatment (p 4266)

HETEROLOGOUS SERUMS AS ANTI INFECTIVE AGENTS (*Continued*)

Diphtheria Antitoxin U S.P
(Lederle Pitman Moore)
Use in diphtheria with penicillin Inject 1000 units subcutaneously for prophylaxis. Give 20 000 to 40 000 units intramuscularly or intravenously for active treatment (p 4302)

Gas Gangrene Antitoxin (Cl. perfringens and Cl. septicum) U S.P
(Cutter Lilly)
Prefer tetanus combined (see below) If given, inject contents of 1 to 4 vials intramuscularly or intravenously (diluted to 300 cc. with saline solution)

Gas-Gangrene Antitoxin (Cl perfringens septicum, novyi sordelli and histolyticum) U S.P
(Lederle)
Prefer tetanus combined (see below) If used, give contents of 1 to 4 vials intramuscularly or intravenously (diluted to 300 cc with sterile saline)

Tetanus Antitoxin (Horse Bovine) U S.P
(Lederle Pitman Moore)
Give 1500 to 5000 units subcutaneously for prophylaxis and 10 000 to 100 000 units intravenously for treatment (diluted to 300 cc with saline solution (p 4564)

Tetanus-Gas Gangrene Antitoxin (Cl. welchii septicum and tetani) U S.P
(Cutter Lederle Lilly National Parke Davis Squibb Wyeth)
To supplement penicillin therapy in infections due to tetanus and other Clostridia (pp 300 and 4341) Inject contents of 2 vials intramuscularly or intravenously (diluted to 300 cc with saline) and repeat as necessary (p 4343)

Scarlet Fever Streptococcus Antitoxin U S P
(Parke Davis Lederle)
Despite efficacy of penicillin, retain in severe toxic infections Give 3000 units for prevention, and 9000 units for treatment. Inject intramuscularly (p 4515)

Staphylococcus Antitoxin N N R.
Obsolete through efficacy of penicillin, aureomycin sulfonamides etc (p 4528)

Anti Anthrax Antibacterial Serum N.N.R.
For use with penicillin streptomycin and aureomycin. Inject 200 cc intravenously with 300 cc saline (p 4198)

Antidysenteric Antibacterial Serum N N R.
(Parke Davis)
Obsolescent through efficacy of chloramphenicol and sulfonamides If used, inject 10 cc intramuscularly for prophylaxis and 20–60 cc intravenously for active treatment after dilution to 300 cc with physiologic saline (p 4520)

Anti Erysipeloid Antibacterial Serum N.N.R.
(Pitman Moore)
Obsolescent through efficacy of penicillin. If used inject intramuscularly 10 cc (p 4322)

Anti Meningococcus Antibacterial Serum U S P
(Parke Davis)
Obsolescent through efficacy of sulfonamides penicillin and aureomycin If used, give 20 000 to 40 000 units intramuscularly or intravenously (after dilution to 300 cc with physiologic saline) (p 4408)

Anti Pneumococcus Type-Specific Antibacterial Serum U S P (Horse Rabbit)
(Lederle Wyeth)
Obsolete through efficacy of penicillin and sulfonamides

Anti H. influenzae B-Antibacterial Serum
(Squibb)
Obsolescent through efficacy of aureomycin chloramphenicol and streptomycin sulfonamide If used give contents of 4 vials (100 mg) intravenously after dilution to 150 cc with saline

Erysipelas-Streptococcus Antitoxin
Obsolete since efficacy of penicillin and sulfonamide

HETEROLOGOUS SERUMS AS ANTI INFECTIVE AGENTS *(Continued)*

Anti Pertussis Hyperimmune Rabbit Serum
(Squibb)
Refined, concentrated globulin fraction Obsolescent through efficacy of aureomycin chloramphenicol polymyxin and streptomycin. If used, inject 4 cc intramuscularly Repeat in twenty four to thirty six hours if necessary

Anti Tularemia Serum
Obsolescent through efficacy of aureomycin, chloramphenicol and streptomycin.

Anti Typhus Serum
Obsolescent through efficacy of aureomycin and chloramphenicol

Anti Rocky Mountain Spotted Fever Serum (Rabbit)
(Lederle)
Obsolescent through efficacy of aureomycin and chloramphenicol If used, inject 60 cc intramuscularly and repeat if necessary

Anti Brucellosis Serum
Obsolescent through efficacy of aureomycin chloramphenicol and streptomycin sulfonamide

Anti Infectious Jaundice (Spirochetal) Serum
Obsolescent through efficacy of penicillin and aureomycin

Anti Plague Serum
To supplement antibiotic therapy

Anti Rabies Hyperimmune Serum
Under investigational use to supplant rabies viru (p 4487)

BLOOD AND BLOOD FORMING ORGANS, NEOPLASMS OF

Tumors of the blood and blood forming organs are being recognized with increasing frequency At times they are diagnosed in the asymptomatic stage from the routine blood count Symptomatic hematopoietic malignancies are recognized in the investigation of asthenia (p 2890) cryptogenic fever in childhood (p 2760) generalized lymphadenopathy (p 1136) cervical lymphadenopathy (p 3518) axillary lymphadenopathy (p 3526) mediastinal lymphadenopathy (p 2804) inguinal lymphadenopathy (p 3092) and splenomegaly (p 1129)

ACUTE LEUKEMIA (FIG 233 P 1104 AND P 1101)

Practical Management

1 Get a complete blood count from the fingertip (p 3696) and make several blood spreads (p 1046)

2 Obtain venous blood for heterophile agglutination (p 468) A negative test repeatedly obtained excludes infectious mononucleosis (Fig 71 p 469 and p 466) a positive test suggests the presence of the benign virus infection with its completely hopeful prognosis

3 If infectious mononucleosis can be excluded refer the patient directly to a hematologist preferably for institutionalization Here in addition to repetition of the blood count further data may be obtained by making spreads from bone marrow obtained through sternal puncture (p 1043)

4 Apply for ACTH which often produces rapid and at least temporary remissions

5 Under close supervision consider subcutaneous or intramuscular injections of aminopterin using daily doses of 0 5 to 1 mg Watch clinical manifestations and peripheral blood count so that the drug may be discontinued on appearance of toxic manifestations including stomatitis melena due to ulceration of the intestinal epithelium anemia thrombocytopenia or complete leukopenia

6 If a remission is obtained with reduction of leukocytes to approximately normal numbers decrease in size of subcutaneous lymph nodes and lessening of hepato-splenomegaly reduce dose and attempt to maintain remission with a lesser amount given at increasing intervals of forty eight to seventy two hours

7 Transfusions may be of symptomatic value but roentgen therapy splenectomy and administrations of potassium arsenite (Fowler s solution) urethane benzol estrogen and androgen offer no hope for benefit

8 As a desperation remedy ACTH and aminopterin failing injection of nitrogen mustard may be considered (p 4439)

CHRONIC LYMPHATIC LEUKEMIA

Practical Management

1 Patients with chronic lymphatic leukemia (Fig 233 p 1104 and p 1102) may live a considerable span of years in contrast to those with acute types of leukemia

2 Roentgen therapy is first choice in practical management and may be conducted ambulatory or in the institution

3 During roentgen therapy frequent blood counts are required If anemia develops transfusions are clearly indicated Treatment must be interrupted if total white count falls below 3600 cells or if thrombocytopenia develops

4 Irradiation sickness may be prevented and mitigated by simultaneous oral administration of aureomycin using doses of 0 5 gm thrice or four times daily

5 When available injections of anterior pituitary corticotropic hormone or of cortisone (adrenocortical hormone) may be considered during or following roentgen therapy

6 Of secondary remedies potassium arsenite (Fowler s solution) is most readily available and holds least threat of toxic reactions Forkner recommends initial doses of 0 3 cc three times daily for two days The do e is preferably given in orange juice immediately after or with meals On the third and fourth days the dose is increased to 0 4 cc three times daily Daily increments are continued until the patient receives a total dose of 0 6 cc three times daily unless toxic symptoms intervene or the leukocyte count approaches normal

7 On the appearance of toxic symptoms or the accomplishment of a normal leukocyte count arsenic is omitted for two to five days At the end of this holiday the maximum dose is repeated and then decrea ed by slow tages until a maintenance dose of 0 3 to 0 4 cc three times daily is reached. This amount is continued indefinitely provided that all is well

8 In the presence of a favorable response to potassium ar enite roentgen therapy again may be resumed occasionally with successful issue

9 With continued roentgen resistance and failure of potassium arsenite P^{32} is next choice since the radioactive isotope may be given orally and toxic symptoms are relatively insignificant

10 Finally all else failing injections of nitrogen mustard merit con sideration despite toxicity (p 4439) At times roentgen resistance dis sipates and a favorable response to irradiation therapy may be obtained Splenectomy and benzol hold no promise for relief

CHRONIC MYELOID LEUKEMIA

Practical Management

1 As in the instance of chronic lymphatic leukemia the patient with chronic myeloid leukemia (Fig 233 p 1104 and p 1102) may survive for a considerable length of time despite massive hepato splenomegaly

2 Roentgen therapy is the therapeutic procedure of choice It may be administered ambulatory or in the hospital

3 The course of therapy must be followed by repeated blood counts The development of anemia requires tran fusion of whole blood With marked leukopenia or thrombocytopenia irradiation therapy must be interrupted Radiation sickness may be prevented and mitigated by simultaneous use of aureomycin in doses approximating 0 5 gm thrice or four times daily Concurrently dramamine in doses of 50 mg four times daily may be employed as in travel sickness (p 4218)

4 In the roentgen resistant consideration must be given to pota sium arsenite (Fowler s solution) urethane P^{32} and nitrogen mustard in approximately that order Splenectomy benzol and aminopterin hold no promise

5 For second choice in the radio resistant potassium ar enite is recommended as in the treatment of chronic lymphatic leukemia (p 4263) Following arsenotherapy irradiation may be subjected to another trial since radio resistance may disappear

6 For third trial in those who have become radio resistant and who fail to respond to potassium arsenite P^{32} is recommended by oral administration

7 For fourth choice the practitioner institutes therapy with urethane using doses approximating 4 cc of the commercial elixir (Abbott) twice daily In the absence of toxic manifestations (anemia leukopenia thrombocytopenia ecchymoses or hematuria) and in the absence of a significant reduction in the total leukocyte count the dose is increased by increments of 4 cc to a maximum of 11 cc four times daily (approxi mately 4 5 gm for the total daily dose)

8 Following urethane therapy roentgen irradiation again may be attempted in the hope that patient resistance has disappeared

9 Finally all else failing nitrogen mustard injections require con

sideration despite the toxicity of the product the patient meantime being fortified with frequent transfusions of whole blood

10 When available treatment with anterior pituitary corticotropic hormone (ACTH) or with cortisone (adrenocortical extract) merits serious consideration since preliminary reports indicate successful though transitory remissions and the toxicity of the hormones is relatively slight compared with other available preparations

POLYCYTHEMIA

Practical Management

1 So successful is administration of P^{32} in the treatment of polycythemia vera (p 1093) that no other form of therapy is comparable Oral administration of doses as small as 5 millicuries may produce remissions lasting for several years at the end of which time the dose may be repeated

2 The ease safety and demonstrable efficacy of P^{32} in the treatment of polycythemia vera relegates to obsolescence previous therapeutic agents including repeated transfusions iron poor diets irradiation urethane nitrogen mustard phenylhydrazin pyrodine benzol arsenic and splenectomy (p 1094)

HODGKIN S DISEASE AND OTHER MALIGNANT LYMPHOMAS (P 1138 AND FIG 237 P 1139)

Practical Management

1 Establish diagnosis by histologic examination of an excised lymph node (p 3935)

2 Obtain chest x rays for determination of extent of mediastinal lymphadenopathy

3 Roentgen therapy is procedure of choice Try to reduce hazard of radiation sickness by concurrent administration of aureomycin 0 5 gm thrice or four times daily and dramamine 50 mg four times daily If anemia develops introduce 500 cc of whole blood In the presence of leukopenia or thrombocytopenia interrupt therapy

4 In the roentgen resistant recourse must be had to injections of nitrogen mustard despite the hazard (p 4439) At the termination of nitrogen mustard therapy irradiation may be resumed in the hope that the tissues have again become sensitive

5 When available anterior pituitary corticotropic hormone (ACTH) and cortisone (adrenocortical hormone) merit thorough trial In preliminary reports at least transitory remissions have been obtained These may serve to tide the patient over when radio resistance has developed Until preparations are commercially available make application for cortisone to Merck and Co Rahway N J or to Dr Chester S Keefer Chairman National Academy Allocation Committee 2101 Constitution Ave Washington D C for ACTH to Dr John R Mote Armour and Co Chicago Illinois Meantime make clinical trials of artisone (Wyeth) and percorten (Ciba) purchaseable in the open market In

the use of the latter inject 1 cc intramuscularly (equivalent to 5 mg desoxycorticosterone) followed within five minutes by intravenous introduction of 10 cc of 10% ascorbic acid (1 gm) Unless prompt and dramatic improvement is noted with artisone and percorten—ascorbic acid abandon therapy after three or four consecutive daily injections

6 Potassium arsenite (Fowler s solution) aminopterin P[32] urethane benzol and splenectomy offer no promise of beneficial re ults

MULTIPLE MYELOMA (P 1126)

Practical Management

1 The prognosis of multiple myeloma unfortunately still remains hopeless

2 The symptoms of multiple myeloma may be controlled by adminis tration of 3 to 6 gm daily of urethane (p 4264) The drug despite its toxicity relieves pain decreases plasma proteins and may cause myeloma cells to disappear from the marrow

3 Urethane failing intravenous or intramuscular injections of 150 mg of stilbamidine with 2% procaine may be tried at daily interval fo 20 to 30 injections

4 Toxic reactions to intravenous stilbamidine include local pain along the course of the vein a feeling of warmth and a fall of blood pressure that may be sufficiently great to produce syncope Delayed toxic reactions include subjective disturbances and dissociated anes thesia of areas supplied by sensory branches of the trigeminal nerve These symptoms may not appear for two to five months after completion of stilbamidine therapy Patients complain of numbness formication heaviness and itching of the affected area The sensation of touch is lost but pain temperature and pre sure modalities remain

5 Gellnorn and Jones (Am J Med 6 202 1949) state that since there is ample evidence that the fundamental lesions are not signifi cantly altered it must be concluded that the drug merely provides symptomatic relief In view of this and the high incidence of drug toxicity on the trigeminal nerve and the protracted duration of the apy we believe that stilbamidine therapy of multiple myeloma should be used only as a last therapeutic resort

BOTULISM

(Limber Neck)

Principles of Diagnosis and Treatment

1 Botulism is one of the few bacterial disturbances relatively unaf fected by recent developments in therapy Essentially the problem is that of neutralizing preformed toxin since clinical manifestations result from ingested poison rather than tissue invasion by Clostridium botulinum

2 Prophylaxis remains the prime endeavor Cl botulinum is an anaerobic sporulent organi m Its destruction requires five hours in

the autoclave Toxin formation is prevented by acidification of contents before canning or preserving Preformed antitoxin is inactivated by boiling for six to fifteen minutes

3 Since commercial canners and preservers have the facilities to avoid contamination of their products the main danger comes from home processing by the hou ewife

4 An official hor.e serum is commercially available (Botuli m antitoxin bivalent (globulin modified) types A and B N N P (Lederle) in vials containing 10 000 units of each type) Under ideal conditions botulinum antitoxin has considerable therapeutic potential Unfortunately under realistic conditions which prevail in clinical practice its usefulness is limited Being a relatively rare condition the first local instance of botulism is rarely diagnosed immediately additionally there is delay in obtaining commercial antitoxin which is rarely stocked because of infrequent demands for its u e finally like other heterologous antitoxic serums (p 4260) administration of botulinum antitoxin must be preceded by determination of hyper ensitivity (p 4187) and desensitization (p 4191) if necessary

Practical Management

Prophylaxis

1 The housewife who does her own canning and preserving must obey the following precautionary measures in the preparation of her products

(a) Preserves must be boiled for five hours before being placed in containers

(b) Before serving home pre.erved products the contents of the container again must be boiled for fifteen minutes to destroy preformed toxin

(c) Preserved food whether in glass or can must be discarded if there are evidences of leakage if the product is our tasting sour melling or obviously decomposed if the can bulges at the end and if there is escape of gas under pressure when the container is opened

2 As soon as the diagnosis of contamination is made by the appearance of the preserve or by recognition of the syndrome of botulism in the first patient local health authorities must be notified Meantime similar products are seized but not destroyed until they can be tested Examinations may be made officially by laboratory methods or crudely and unofficially by feeding the preserve to a single chicken Following an incubation period of twelve to thirty six hours the fowl develops limber neck after which it is destroyed and completely burned by incineration

3 While similar products are being ought and seized all other individuals who may have eaten the contaminated product are warned to seek medical advice and prophylactic therapy through injection of antitoxin as de.cribed under Immediate Care

Immediate Care

1 As soon as the diagnosis is suspected send an urgent call for antitoxin While waiting test the patient and others who have ingested toxin for reactions to horse serum Desensitize hyperreactors (p 4191)

2 Administer antihistamine for the combined purpose of prophylaxis in the event that serum is to be administered and also for sedation without danger to the respiratory mechanism Inject 1% benadryl intramuscularly in the amount of 5 cc (50 mg) or give orally 100 mg of pyribenzamine or benadryl with repeat doses of 50 mg every three or four hours for the first day

3 Instruct the patient to spit out saliva or provide with a saliva ejector as used in dentistry

4 If the patient has been seen within a few hours of ingestion of the suspected product consider gastric lavage or induction of emesis by ipecac (p 1757) However if the patient swallowed the suspected food longer than twelve hours before the diagnosis has been made or if there are already evidences of paralysis avoid gastric lavage and emesis lest aspiration into the lungs be produced

5 If the patient has been seen within six to eight hours following ingestion of the suspected food give a saline cathartic Otherwise prefer an enema or a colon irrigation that will not so greatly fatigue and dehydrate the sufferer

6 Deposit 100 000 units of crystalline penicillin G and 300 000 units of procaine penicillin G for prophylaxis in the event of an aspiration pneumonitis

7 If there are beginning evidences of respiratory difficulty place the patient in an oxygen tent and provide for artificial respiration if needed

8 If it is at all possible avoid sedatives analgesics and opiates since these may further depress the respiratory center

9 While awaiting the arrival of serum set up an intravenou drip if the patient is prostrated and/or dehydrated as the result of vomiting and diarrhea Initially use 5% dextrose in saline

10 When antitoxin arrives make a decision as to the wisdom of using heterologous serum Weigh the severity of the illness against the degree of existing hypersensitivity

For prophylaxis in the asymptomatic known to have ingested toxin give an initial intramuscular deposit of 2500 to 5000 units with 5 cc of 1% benadryl

For active treatment set up an intravenous drip (p 3775) After prophylactic antihistamine (5 cc of 1% benadryl) infuse at least 100 000 units of botulinum antitoxin diluted to 500 or 1000 cc with 5% dextrose in isotonic saline solution Follow serum by intravenous administration, through the drip of an additional dose of 5 cc of 1% benadryl During the intravenous drip keep available another syringe with 2 cc of epinephrine chloride (1 1000) for introduction if evidences of anaphylaxis develop

Continuing Care (Unfavorable Course)

1 Since toxin is destroyed within the body within the cour e of a few days continue all heroic efforts without interruption If the life of the patient can be preserved for only a few days recovery is almost completely assured Repeat antitoxin as previously de cribed preceded and followed by antihistamine

2 In the event of worsening conditions try to avoid panic medica tion that can only add to the patient s burden Sedatives and opiates tend to increase respiratory depression and undue amounts of stimu lants increase the patient s awareness of difficulties and add the ele ments of anxiety and fear

3 Since the principal danger is respiratory depression place main reliance on oxygenation and artificial respiration (p 3766) Very little respiratory stimulation is accomplished by caffeine strychnine ephe drine or the sympathomimetic amines such as epinephrine etc How ever if the course is progressively unfavorable try intravenous injections of 1 cc of metrazol (0 1 gm) or 3 cc of nikethamide (coramine)

BOUTONNEUSE FEVER

[Exanthematous Fever Eruptive Fever Marseilles Fever Fever of Conor and Bruch]

Principles of Diagnosis and Treatment

1 Boutonneuse fever (p 383) is a rickett.iemia resembling typhus fever (p 4621)

2 The disease is tick borne It is characterized by an almost con stant appearance of a maculo papular eruption of the palms and soles and a tache noire (black spot) usually at the site of the tick bite (p 383)

3 The causative agent Dermacentroxenus conori resembles D rickettsii The dog tick Rhipicephalus anguineus is the principal if not the only vector of D conori

4 Whereas guinea pigs recovered from Rocky Mountain spotted fever are solidly immune to boutonneu e fever spotted fever vaccine gives no protection against human boutonneuse fever However an attack of boutonneuse fever confers an immunity of at least two months

5 The Weil Felix reaction occurs late in the course of the disease appearing at the end of the first or beginning of the second week of convale cence It may be positive in equal titers for both Proteus OX 19 and OX 2 With purified washed rickettsial antigen boutonneuse fever may be differentiated from spotted fever by the complement fixation reaction

6 After an incubation period of five to seven days the onset is usually sudden with chill and a rise in temperature often above 104° F Usually at the time of on et there is a small ulcer about 2 to 5 mm in diameter with a black necrotic center surrounded by a darker red dish area of variable dimensions This probably represents the site of

the tick bite Associated symptoms at onset are violent and persistent headache lassitude joint pains and coated tongue

7 Three or four days after the onset a maculopapular eruption is seen spreading rapidly over the whole body but involving principally palms soles and face

8 After a febrile period of eight to fourteen days the temperature usually falls by rapid lysis The case fatality rate is less than 3 per cent

9 Because of its resemblance to typhus fever there is reason to believe that boutonneuse fever will respond specifically to aureomycin chloramphenicol and para aminobenzoic acid

Practical Management

Prophylaxis

1 No vaccine is currently available
2 Elimination of the dog tick removes the only known vector

Immediate Care

[See Typhus Fever]

BRONCHIAL ASTHMA

In the management of bronchial asthma the physician s urgent obligation is symptomatic relief of acute distress During intervals of freedom from attack efforts are made to prevent recurrence by elimination of bacterial and nonbacterial sensitizing agents (p 4176) desensitization of hyposensitization with offending allergen (p 4180) psychotherapy (p 4180) and prophylaxis or palliation with antihistamines and adrenergens (p 4158)

Practical Management

Immediate Care

1 Order tablets of plain antihistamines such as pyribenzamine or *benadryl in doses of 100 to 150 mg every two or three hours* or combine with oral adrenergen *as in histadyl ephedrine capsules*

2 Spray with 1 100 epinephrine

3 If no response try sublingual administration of isuprel in doses of 10 to 15 mg Caution the patient not to swallow tablet Observe first dose carefully watching for toxic side effects such as tachycardia elevation of blood pressure etc

4 Inject intramuscularly 2 to 5 cc of 1% benadryl (20 to 50 mg)

5 Deposit subcutaneously 0 2 to 0 5 cc of 1 1000 epinephrine hydrochloride noting sympathomimetic effect as above

6 Give a slow intravenous injection of 0 3 to 0 6 gm of aminophyllin

7 These efforts failing try intravenous introduction of 2 to 5 cc of benadryl made up to 20 cc with sterile saline or distilled water

8 Avoid expectorants sedatives opiates and atropine like drugs Most asthmatics have marked drug idiosyncrasy and often develop serious untoward manifestations

9 Apply for ACTH which may be promptly effective

Continuing Care (Unfavorable Course)

1 Administer oxygen by mask method

2 Try intravenous injection of 0 5 to 1 cc of 1 10 000 epinephrine hydrochloride

3 If oxygen mask is ineffectual transfer patient to tent preferably equipped to deliver gas by positive pressure

4 If still refractory obtain helium oxygen mixture

Continuing Care (Progressively Unfavorable Course)

1 In desperation summon bronchoscopist for endoscopic lavage and aspiration of mucous plug

2 Try an intravenous infusion of 100 cc of 1% procaine diluted to 500 cc of normal saline or distilled water

Interval Treatment

Between attacks seek to eliminate offending allergen by providing an allergen free atmosphere hyposensitization or desensitization particularly in pollinoses climatic change or use of air conditioning and air filtration antibiotic treatment of bacterial foci and surgical elimination and drainage of accessible foci

BRUCELLOSIS

[Bang s Disease Malta Fever Mediterranean Fever Melitensis Rio Grande Fever Texas Fever Undulant Fever]

General Principles of Diagnosis and Therapy

1 Brucellosis is widely disseminated among domestic animals and particularly cattle pigs and goats The majority of human infections result from handling infected animals and from ingestion of food products that have not been properly processed The transmission of brucellosis from one human being to another is probably rare

2 Major responsibility for control of brucellosis rests with public health authorities These officials are faced with the same diagnostic problems as the practitioner Using presently available methods they can detect only a small percentage of the numbers of infected animals Then the diagnosis being established their only recourse is to sacrifice and slaughter livestock This gross method of attacking the problem cannot eradicate the vast reservoirs of brucellosis prevalent throughout the United States

3 Individual efforts at prophylaxis must be used to supplement

public health measures Hou^ewife and farmer can accomplish much by simple pa^teurization of milk used for drinking purposes and for preparation of dairy product^ Brucellosis is much more prevalent in rural districts where the farmer provides raw fresh milk for his own table and for local cu tomers than in large urban communities where there is official public supervision of dairy products and compulsory pasteurization

4 Diagnosi^ of brucellosis is rarely made It is provided only by growth of organism from blood stream sternal bone marrow tissue fluid or pus M melitensis grows best in tryptose phosphate broth with oxygen replaced by 10 to 20% carbon dioxide

5 Whereas the bacteriologic diagnosis can be made in approximately 25 per cent of acute infections it is exceptional to demonstrate the organism in the much more prevalent chronic types of invasion

6 The presumptive diagnosis of brucellosis rests on clinical and laboratory data The brucellosis minded detect the disease in every otherwise undiagnosed illness that comes within the scope of their observation At the other extreme those who have not been impressed by more recent knowledge of the extensive dissemination of the disease regard brucellosi as a rare and exotic infection

7 Laboratory evidence of brucellosis rests on skin sensitivity agglutination reactions opsonocytophagocytic index and blood counts Skin sensitivity is best detected by using commercially available brucellergen (Sharp & Dohme) marketed in vials which must be refrigerated when not in use and thoroughly shaken prior to withdrawal of fluid The test is performed by injection of 0 1 cc intradermally on the flexor surface of the forearm The po itive reaction is a circumscribed erythema with edema and induration varying in diameter from 2 to 10 cm and persisting for as long as seven days (Fig 45 p 318) The official reading is made at the end of forty eight hours at which time an erythema exceeding 2 cm in diameter may be considered indicative of sensitivity to melitensi^ protein

8 In addition to the local reaction the intradermal test may provoke a systemic response including elevation of rectal temperature reading above the pre test level and exacerbation of focal manifestations

9 The presence of a positive reaction indicates merely that the *individual has become sensitized to the protein of the organism It does* not mean necessarily that he suffer^ from the disease or that the presenting symptoms during the current illne^s are in any way related to skin sensitivity

10 Before skin sensitivity is tested withdraw blood for serologic reactions Regard an agglutination titer in exce ^ of 1 100 with high suspicion particularly if reaction is done with antigen supplied by Bureau of Animal Industry Of greatest significance is a rising ti'e^ una sociated with use of vaccine or repeated skin tests

11 The agglutination reaction is not oracular The test is often negative in acute phases of disease and in many who have long suffered from chronic brucellosis A high titer may be misleadingly present in

those who have had the disease and recovered and who at the time of the testing are not necessarily suffering as the result of previous infection

12 Cross agglutinations may be caused by prophylactic vaccination with cholera vibrio

13 As in the case of all other laboratory data the agglutination test requires interpretation in terms of clinical phenomena The association of a rising titer with skin sensitivity and clinical manifestations con sistent with the presence of the disease furnishes strong presumptive evidence that the patient suffers from an invasion by Brucella abortus or one of the members of its bacterial family

14 The opsonocytophagocytic index is difficult to de ermine and results are unreliable

15 Of some presumptive diagnostic evidence is the presence of leukopenia with relative lymphocytosis

16 Clinical manifestations of brucello is are as varied as those of tuberculosis (p 314) Acute brucellosis may occur as a generalized systemic invasion simulating influenza or typhoid fever Under these circumstances it may or may not be characterized by remissions and exacerbations described as characteristic of undulant fever Systemic manifestations may give way to evidences of localization in skeletal system (p 314) digestive system (p 315) central nervous system (p 315) respiratory system (p 316) endocardium or reproductive system (p 316)

17 Acute brucellosis may terminate uneventfully but most often it passes into the chronic phase The latter may or may not have been preceded by demonstrable acute invasion

18 *Chronic* brucellosis is even more ill-defined than the acute form It may be characterized by such vague symptoms that the patient is cla sified as a neurasthenic or its course may be punctuated by exacerbations involving any of the systems to which reference was previously made Thus some clinicians credit chronic brucellosis as the etiologic mechanism in many otherwise ill-defined clinical entities calling attention to the high incidence of skin sensitivity in patients with multiple sclerosis Others assume that brucellosis is probably an etiologic factor in uveitis

Practical Management

Immediate Care

1 Treat acute brucellosis according to the general principles established for the management of a generalized infection (p 68) Chronic brucellosis may be handled in an ambulatory manner

2 In acute brucellosis give an immediate priming dose of aureomycin or chloramphenicol approximating 50 to 100 mg per kilogram of body weight (3 5 to 7 gm for the average adult weighing 150 pounds)

3 For synergistic effect supplement aureomycin or chloramphenicol with streptomycin Inject intramuscularly 1 or 2 gm of streptomycin for the initial dose

4 In chronic brucellosis begin with exceedingly small doses in order to avoid Herxheimer like reactions Start with 25 mg four times daily on the second day increase to 150 mg four time daily, on the third day to 400 mg four times daily on the fourth day to 500 mg four times daily on the fifth day to 1 gm four times daily and on the sixth day to the full amount of 1 5 gm four times daily to total 6 gm or 24 capsules each containing 250 mg of aureomycin or chloramphenicol

Continuing Care (Favorable Course)

1 In acute brucellosis continue with aureomycin or chloramphenicol and streptomycin for a minimum period of two weeks Because of the tendency of brucellosis to be recurrent or chronic it is perhaps better to extend the treatment course for three weeks Request the patient to return after a few months for re treatment if necessary

2 Continue treatment in chronic brucellosis with aureomycin or chloramphenicol supplemented by streptomycin, for a minimum period of three weeks Have the patient report again at the end of three months if all is well Consider re treatment for prevention of recurrence or exacerbation

Continuing Care (Unfavorable Course)

1 If the patient is intolerant of aureomycin substitute chloramphenicol or terramycin in somewhat larger dosage

2 If the patient is intolerant of streptomycin substitute dihydro streptomycin or neomycin in somewhat larger dosage

3 With continued signs of infection or recurrence, add sulfonamides to the combination of oral administration of aureomycin or chloramphenicol and of intramuscular injections of streptomycin Give a loading dose of 2 gm each of sulfadiazine and sulfamerazine with 4 gm of bicarbonate of soda Maintain sulfonamide levels by daily doses of 0 5 gm of each every four hours for at least two weeks and preferably longer Watch for evidences of drug toxicity or idiosyncrasy by clinical observation urine analysis and repeated blood counts

4 Made obsolete by successful antibiotic therapy are brucellosis antibacterial heterologous serum (prepared by Foshay from horses) convalescent human homologous antibrucellosis serum and the various commercially available brucella vaccines (Lederle Pitman Sharp & *Dohme National Drug) These last are suspensions containing* 2000 million organisms per cc Presently useless for curative purpose they still possess value for preventive inoculation

CAMOQUIN

Camoquin is a synthetic antimalarial with the formula 4 (7 chloro 4 quinolylamino)-alpha-diethylamino ortho-cresol

Available Products

Tablets containing 50 mg For experimental use only

Therapeutics

In vivax malaria fever and peripheral blood parasites disappear after third or fourth treatment-day In falciparum malaria fever dis appears on third to fifth day asexual parasites disappear between second and fourth days and sexual parasites between ninth and nine teenth days

Camoquin seems to have slight or no influence on crescent forms but it has a decided effect on vivax gametocytes and on asexual forms of vivax and falciparum

Toxicology

Camoquin has no undesirable secondary effects

CANICOLA FEVER

Canicola fever is a leptospirochetosis transmitted by dogs It closely resembles spirochetal jaundice and is managed similarly placing main reliance on penicillin

CARINAMIDE (STATICIN)

[Caronamide]

Carinamide (staticin) (4 carboxy phenylmethanesulfonanilide) is a white crystalline powder sparingly soluble in water

Available Products

Staticin Carinamide Tablets (Sharp & Dohme) 0 5 gm

Pharmacology

Carinamide was introduced in 1947 for the purpose of maintaining high and sustained blood levels of penicillin through the production of a temporary renal blockade

In its elimination through the kidneys 80% of penicillin passes through the tubules and 20% through the glomeruli By competing with penicillin for combination with the enzyme responsible for tubular excretion of antibiotic carinamide blockades the principal renal excre tory mechanism As a result penicillin blood levels are increased three or fourfold and prolonged in approximately the same ratio

The renal blockade produced by carinamide is reversible Following elimination of enzyme compound the enzyme is freed and thenceforth transports penicillin through the tubular epithelium according to the normal pattern of renal elimination In doses sufficient to suppress tubular elimination of penicillin carinamide has no significant by effects on heart respiration blood pressure or renal volume

Despite the advantages of carinamide newer repository penicillins

4 In chronic brucellosis begin with exceedingly small doses in order to avoid Herxheimer like reactions Start with 25 mg four times daily on the second day increase to 150 mg four times daily on the third day to 400 mg four times daily on the fourth day to 500 mg four times daily on the fifth day to 1 gm four time daily and on the sixth day to the full amount of 1 5 gm four times daily to total 6 gm or 24 capsules each containing 250 mg of aureomycin or chloramphenicol

Continuing Care (Favorable Course)

1 In acute brucellosis continue with aureomycin or chloramphenicol and streptomycin for a minimum period of two weeks Because of the tendency of brucellosis to be recurrent or chronic it is perhaps better to extend the treatment course for three weeks Pequest the patient to return after a few months for re treatment if neces ary

2 Continue treatment in chronic brucellosis with aureomycin or chloramphenicol supplemented by streptomycin for a minimum period of three weeks Have the patient report again at the end of three months if all is well Consider re treatment for prevention of recurrence or exacerbation

Continuing Care (Unfavorable Course)

1 If the patient is intolerant of aureomycin substitute chloram phenicol or terramycin in somewhat larger dosage

2 If the patient is intolerant of streptomycin substitute dihydro-streptomycin or neomycin in somewhat larger dosage

3 With continued signs of infection or recurrence add sulfona mides to the combination of oral administration of aureomycin or chloramphenicol and of intramuscular injections of streptomycin Give a loading dose of 2 gm each of sulfadiazine and sulfamerazine with 4 gm of bicarbonate of soda Maintain sulfonamide levels by daily doses of 0 5 gm of each every four hours for at least two weeks and preferably longer Watch for evidences of drug toxicity or idiosyncrasy by clinical observation urine analysis and repeated blood counts

4 Made obsolete by successful antibiotic therapy are brucellosis antibacterial heterologous serum (prepared by Foshay from hor es) convalescent human homologous antibrucellosis serum and the various commercially available brucella vaccines (Lederle Pitman Sharp & Dohme National Drug) These last are suspensions containing 2000 million organi ms per cc Presently useless for curative purpo e they still possess value for preventive inoculation

CAMOQUIN

Camoquin is a synthetic antimalarial with the formula 4-(7 chloro-4 quinolylamino)-alpha-diethylamino-ortho-cresol

Available Products

Tablets containing 50 mg For experimental use only

3 At roll call the next morning administer a third prophylactic dose This routine affords protection against chancroid and gonor rhea but not against other venereal diseases (p 4351) It will not mask a syphilitic invasion

Immediate Care

1 For specific anti infective therapy the practitioner has the choice of sulfonamide streptomycin or aureomycin chloramphenicol for the cure of chancroid Either of the last named is distinctly preferable since each is absorbed orally and lacks significant toxicity By contrast sul fonamide has potential toxicity and streptomycin requires hypodermic administration

2 If sulfonamide is used prescribe an initial dose of 2 gm each of sulfadiazine and sulfamerazine with 1 teaspoonful of sodium bicar bonate For maintenance doses order 0 5 gm each of sulfadiazine and sulfamerazine every four hours for three days Thereafter prescribe 0 5 gm of each every six hours for two weeks unless toxic manifesta tions develop Urine examinations and blood counts are made at least twice weekly during sulfonamide administration

3 Streptomycin therapy requires intramuscular injections of 0 5 gm every six hours for five days This routine virtually precludes ambula tory treatment

4 Except on grounds of economy aureomycin chloramphenicol therapy constitutes the method of choice Oral doses of 500 mg (2 products) are given immediately Maintenance doses of a single prod uct (250 mg) 4 times daily for two weeks suffice to give almost 100 per cent cure with negligible toxicity Sulfonamide therapy has the single advantage that is is less expensive

5 Local treatment is aimed primarily at cleanliness and avoidance of masking the hard chancre (Fig 48 p 335) The parts are merely cleaned with soap and water If necessary the preputial cavity is irri gated with saline solution or with potassium permanganate of a strength no greater than 1 8000

6 In the event that the inguinal bubo becomes sore and tense aspira tion is performed when the lesion becomes fluctuant Incision however is not advised

7 For prophylaxis of possible coincidental syphilis the patient receives at least 6 000 000 units of penicillin Crystalline procaine penicillin G suspended in oil with 2% aluminum monostearate is deposited intramuscularly over a span of ten days according to the convenience of patient and physician If the patient can be seen daily 600 000 units are injected at each visit

8 Approximately six weeks after the chancroidal lesion is healed the patient returns for a follow up visit at which time serological tests for syphilis are repeated

9 At the end of another six weeks or three months after acquisition of the infection tests are again repeated and the patient is circumcised if necessary

(and especially the salt of crystalline procaine penicillin G) renders obsolete the method of renal blockade It is unlikely that carinamide will be retained for clinical use except in serious exigencie when less cumbersome methods have failed

Toxicology

Occasionally carinamide produces nausea and vomiting These symptoms are minimized by crushing tablets and administering them with food or alkali On rare occasions carinamide has produced drug fever and a toxicoderm A reducing substance that is not glucose may be noted in the urine

Carinamide does not effect the excretions of streptomycin or sulfonamides Its utility is limited completely to its effect on penicillin

CHANCROID

[Soft Chancre]

Principles of Diagnosis and Treatment

1 The diagnosis of soft chancre is usually made clinically (p 288)

2 For confirmation spreads prepared from lesions are stained with methyl green pyronin (Pappenheim) They reveal H ducreyi as a small ovoid rod free or within phagocytes arranged in pairs or group

3 Available also is the Ito Reenstierna skin test (Fig 41B p 289) made with 0 1 cc Lederle Ducrey Antigen (p 4206)

4 Despite confirmation of H ducreyi as the etiologic agent in the production of the venereal ulcer the practitioner must suspect simultaneous or coincidental infection with Tr pallidum of syphilis (p 331) The incubation of soft chancre may be as brief as three days whereas the hard chancre may not appear for several weeks during which time serologic tests are completely and misleadingly clear (p 337) The patient who acquires a chancroidal and a syphilitic infection at a single exposure may be cured of the lesser infection before the graver invasion becomes manifest

5 H ducreyi is sensitive to sulfonamide streptomycin aureomycin and chloramphenicol

Practical Management

Prophylaxis

In military establishments the incidence of chancroidal infection has been diminished from 52 to 6 per thousand by institution of the following routine

1 On issuance of the overnight pass give each soldier 2 gm of sulfadiazine or sulfamerazine
2 On return to quarters repeat dose

4 Nonsuppurative encephalomyelomeningitides (p 442) are infre quently observed following varicella although Van Bogaert reports 64 instances occurring over a span of eighteen years Quite possibly the complication is a hypersensitivity phenomenon Because of its gravity and unpredictability consider prophylactic antihistamine therapy using daily doses of 200 mg of pyribenzamine or benadryl particularly in those with known allergy

CHLORAMPHENICOL

[Chloromycetin]

Chloramphenicol is a potent antibiotic isolated in nature from cul tures of Streptomyces venezuelae The formula of chloramphenicol D () threo 1 p-nitrophenyl 2 dichloroacetamido 1 3 propanediol reveals several unique features it is the first compound containing a nitro group (NO_2) or a dichloroacetic acid residue ($OOCCHCl_2$) to occur free in nature and it is the first major antibiotic to be synthesized on a practical scale Natural and synthetic chloramphenicols are identical in chemical physical and clinical properties

Available Products

Kapseals Chloromycetin (Parke Davis) 250 mg

Suppository in water soluble base for rectal in ertion in infancy and childhood particularly and for adults with gastric intolerance or inability to swallow

Bacterial Spectrum

The bacterial spectrum of chloramphenicol is almost identical with that of aureomycin (p 4242) Quantitative variations occur as for example the greater sensitivity of typhoid and salmonellae (paraty phoid) to chloramphenicol and of gram negative cocci and brucellae to aureomycin These differences however are minor compared to the close parallelism that exists between the two in most other respects

Pharmacology

Chloramphenicol is presently available only for oral administration and rectal insertion The latter route may be used by introducing punc tured cap ules or a water soluble suppo itory base After an effectual dose maximum blood levels are reached at the end of two hours Levels steadily decline until after eight hours none is detectable Urine levels are appreciable at two hours but decline rapidly over the course of the next ten hours With blood levels of 15 micrograms per cc the concentration of chloramphenicol in spinal fluid reaches 4 to 12 micrograms within three hours

CHENOPODIUM, OIL OF (N F)

Oil of chenopodium previously was used extensively as an anthelmintic in ascariasis and trichuriasis Because of its toxicity it has been mostly superseded by hexylresorcinol and tetrachlorethylene

Available Product

Oil of Chenopodium N F 0 3 or 0 6 cc

Therapeutics

When given for anthelmintic effect the undernoted routine is suggested

1 For one week preceding treatment take full diet avoiding alcohol and fats

2 On the night before treatment take a saline purge

3 On the morning of treatment administer 0 6 or 0 9 cc of oil of chenopodium with a glass of milk

4 Repeat the dose once or twice at half hour interva s to total 1 2 to 2 7 *cc*

5 Two hours after the last dose repeat the saline purge

Toxicity

See p 1896

CHICKENPOX

[Varicella]

Principles of Diagnosis and Treatment

The virus of chickenpox is a filtrable organism which appears re is tant to antibiotics Fortunately the disease is self limited and rarely has significant complications other than an occasional encephalitis (p 4307)

Practical Management

1 No specific antibiotic therapy is available for the prevention or cure of chickenpox (Fig 67 p 421) Vaccination with material from lesions has not proved effectual Injection of gamma globulin is wasteful Intramuscular deposits of 15 to 20 cc of convalescent serum require efforts not warranted in routine practice

2 While it is not recommended that children be exposed deliberately to chickenpox no great effort should be expended to prevent the disease As a matter of fact the long incubation period makes prophylactic measures as useless as they are impractical

3 Protect children with weakened resistance from secondary infection of vesicles by daily intramuscular injections of 100 000 units of crystalline procaine penicillin G in aqueous suspension or by addition of 50 000 units of penicillin G four times daily to milk soup or sweetened drinks

CHLORGUANIDE HYDROCHLORIDE

[Guanatol Hydrochlorid^ Paludrine SN 12837]

Chlorguanide a synthetic antimalarial with the formula N_1 (p chloro phenyl) N_5 i opropylbiguanide is available as a white odorless and slightly bitter powder and shares with chloroquine the distinction of being currently the best and the least toxic antimalarial (p 4397)

Available Products

Chlorguanide Hydrochloride Tablets N N P (Abbott) 100 and 300 mg
Guanatol Hydrochloride Tablets (Lilly) 25 50 and 100 mg

Pharmacology

After oral do es approximately 60% of chlorguanide is ab orbed with maximum plasma concentrations in approximately two hours Following ab orption chlorguanide localizes in ti sues to only a slight degree but it does not tend to accumulate except when given in lethal doses

Chlorguanide must undergo ome metabolic alteration in the body ince excretion by feces and urine is incomplete Approximately 10% of the oral dose appears in the stool and 20 to 30% in the urine Despite the fact that only 30 to 40% of the total oral dose is thus accounted for tissue accumulation does not occur It mu t be concluded that some alteration of the nucleus occurs within the body

In man the minimum effective plasma level is probably less than 1 microgram per 100 cc Do es as small as 50 mg twice daily give a plateau concentration between 5 and 15 micrograms per 100 cc so that relatively small quantities of the drug are required for effectual action

Toxicology

Therapeutic doses of chlorguanide produce no significant toxic manifestations or untoward side reactions in man Larger doses such as 1 gm daily used for investigational purposes may cause vomiting epigastric pain hematuria and e ophageal spasm

Therapeutics

Chlorguanide is the only causal prophylactic available in malaria Unfortunately this extraordinary therapeutic effect does not hold for all malarial parasites but can be demonstrated only for P falciparum (malignant tertian) This property makes chlorguanide first choice in the causal prophylaxis and radical cure of *falciparum malaria* It is useful also in vivax malaria (benign tertian) where it controls acute attacks and suppre ses relapses In vivax malaria chlorguanide is not as effective as chloroquine or quinacrine to which it yields preference

The antimalarial activity of chlorguanide in falciparum and vivax malaria may be summarized as follows

Toxicology

No important symptoms or signs of toxicity have been observed thus far as the result of chloramphenicol administration An occasional patient develops nausea and vomiting but this is infrequent and transitory as compared to aureomycin (p 4242)

Antitherapeutic Devices

So far as is presently known chloramphenicol is conspicuously free from Antitherapeutic devices (p 4131) Bacterial fastness (p 4132) has not yet been encountered acute histamine type hypersensitivities (p 4168) are infrequent and chronic tuberculin type manifestations (p 4169) have not been reported

Therapeutics

The wide bacteriologic spectrum indicates the broad effectiveness of chloramphenicol (p 4242) Because of their close parallelism a single chart has been prepared to suggest joint indications for aureomycin and chloramphenicol (p 4243) *As has been previously intimated* the two antibiotics may be used interchangeably except in typhoid fever shigelloses and salmonelloses where chloramphenicol is distinctly the preparation of choice and in gram negative invasions and brucellosis where aureomycin is patently superior In point of fact future experience may reveal the wisdom of combining both anti infective agents in the manner in which various sulfonamides are presently administered (p 4541)

Dosage

Dosage schedules for aureomycin are applicable also to chloramphenicol In general hyperacute infections require a heavy loading dose of 50 to 100 mg per kilo (approximating 3 5 to 7 gm for the average adult weighing 150 pounds) in chronic low grade *infections* as little as 25 to 60 mg per kilo suffice for the priming or loading dose (2 to 4 gm for the average adult weighing 150 pounds)

Maintenance doses in general average 1 or 2 capsules (250 to 500 mg) every three four or six hours depending on the severity of initial symptoms and the therapeutic response Following acute phases of the disease and defervescence it is suggested that maintenance doses be continued for several days to prevent relapse or recrudescence

Comparison with Other Antibiotics

Like aureomycin chloramphenicol may be given with penicillin sulfonamides and a streptomycin for broader coverage of the bacterial spectrum in Probatory and Desperation Anti infective Therapy

The choice between chloramphenicol and aureomycin is based on trivial differences for the most part (p 4242) When in doubt the practitioner may wisely decide to use both preparations each in half the dosage indicated in afore mentioned schedules

CHLOROQUINE DIPHOSPHATE N.N.R.

[Aralen Sontochin Pesochin S N 7618]

A potent and relatively non toxic all purpose antimalarial and ame bacide with the formula 7-chloro-4(4-di-ethylamino-1 methylbutylamino) quinoline diphosphate

Available Product

Aralen Diphosphate N N R Tablets (Winthrop) 250 mg

In addition to commercially available tablets intramuscular injections of 0 2 gm in 5 cc of sterile aqueous solution have proven effective in vivax and falciparum malaria

Pharmacology

Chloroquine posse ses more than 8 times the cu.ative potency of quinine It is more than 3 times as active as quinacrine

Therapeutics

Chloroquine is highly active against erythrocytic forms of P vivax and P falciparum With chlorguanide it is the best and least toxic all purpose antimalarial

In falciparum malaria it abolishes the acute attack and effects a complete cure though it yields to chlorguanide as the p eparation of choice since the latter is also a causal prophylactic

Chloroquine is the preferred drug in the treatment of vivax and quartan malaria In these infections it is not prophylactic but it is sup p es ive and lengthens the span between treatment and relapse In the management of vivax relapses however it yields to the combination of pentaquine and quinine (p 4398) For more rapid antipyretic effects in hyperacute malarias quinine is more effective

In the malarial infections the principal action of chloroquine is on endo erythrocytic forms namely trophozoites and schizonts

Chloroquine is also useful as an amebacide It is effectual against both intra inte tinal and extra intestinal forms but particularly the latter Therefore it may well replace the more toxic emetine (p 529)

Dosage

Suppression of vivax malaria 500 mg (2 tablets) twice a week

Treatment of acute vivax or falciparum malaria Initial dose of 1 gm (4 tablets) followed by 0 5 gm at 6 24 and 48 hours to total 2 5 gm (10 tablets)

Prophylaxis of amebiasis 250 mg twice a week

Treatment of amebiasis 250 mg twice daily for two to three weeks

Toxicity

Chloroquine is well tolerated in therapeutic doses On rare occasions there may be mild headache itching visual and gastro-intestinal dis

(a) By destruction of pre erythrocytic forms of P falciparum it produces radical cure of acute attack it accomplishes causal prophylaxis in that the patient remains symptom free after discontinuance of the drug it prevents mosquito transmission of P falciparum infection within a few hours after the oral dose is administered

(b) In vivax malaria chlorguanide terminates the clinical attack by its action on asexual erythrocytic forms (early schizonts) but parasites reappear after discontinuance of the drug Hence in vivax malaria though chlorguanide effects cure of the acute attack and suppresses activity while the drug is being administered it is not a causal prophylactic Seizures reappear once the drug has been discontinued and mosquito transmission through bite o the patient during therapy is not prevented as in the case of P falciparum infections

Dosage

For causal prophylaxis of P falciparum 300 mg twice weekly

For active treatment of falciparum malaria 100 mg 3 times daily for ten days Thereafter for suppression 300 mg twice weekly

For active treatment of vivax malaria 100 mg 3 times daily for two to three weeks Thereafter suppressive doses of 100 mg thrice weekly for six months For treatment of relapsing vivax malaria prefer pentaquine quinine combination (p 4398)

CHLOROPHYLL

Soluble derivatives of chlorophyll accelerate healing stimulate tissue growth and cell metabolism inhibit anaerobic proteolytic bacterial growth aid in controlling superficial infection and deodorize foul wounds

Available Products

Chloresium ointment (Rystan) *chloresium solution* (Plain) *chloresium solution* (Nasal) *chloresium solution* (*aerosol*) for use with penicillin and other antibiotics *chloresium dental ointment*

Therapeutics

For local application to wounds ulcers fistulas burns sinuses amputation stumps tooth sockets etc as nasal spray or aerosol with penicillin or other antibiotics

The use of chloresium aerosol solution instead of physiological saline solution as diluent for penicillin results in higher antibiotic levels due in part to inhibition of penicillinase as by chlorophyll

6 Since protection from cholera vaccine requires at least ten days for development of an effectual active immunity prescribe soluble sul fonamide (sulfadiazine or thalamyd in doses u ed for Continuing Care) to sterilize intestinal content while antibodies are developing

Immediate Care

1 Because of the gravity of the di ease inaugurate therapy in cholera by intravenous medication Set up an intravenous drip and inject sodium sulfadiazine and/or aureomycin hydrochloride Of the former give a priming dose of 5 gm followed by no less than 500 cc of physio logic saline and 500 cc of plasma If the patient has been depleted by fluid lo s through vomiting and diarrhea continue intravenous drip for introduction of fluid saline plasma and antibiotic

2 If aureomycin is used introduce 500 mg in 0 75% sodium carbonate

Continuing Care (Favorable Cour.e)

1 For continuing care the practitioner has choice of oral sul fadiazine sulfaguanidine thalamyd preparation 6257 aureomycin or chloramphenicol

2 Concerning the various sulfonamides there is a difference of opinion among experts concerning aureomycin and chloramphenicol there is insufficient experience for expre sion of any dogmatic opinion

3 As to sulfadiazine Indian authorities report no appreciable effect yet participants in a symposium on the treatment of cholera agreed that given early in the disease sulfadiazine with intravenous infusions of plasma may be depended on to be 100 per cent effective in assuring the recovery of the patient If the practitioner decides to continue sulfadiazine after the intravenous priming dose he may inject intravenously 2 5 gm of the sodium alt once or twice daily depending on the course of the disease and the patient respon e If the stomach is tolerant he may give 1 gm four times daily with sodium bicarbonate

4 Those Indian medical authorities who had such unfavorable experiences with sulfadiazine concluded that sulfaguanidine was of considerable value In their experience administration of insoluble sulfonamide reduced gross mortality from 7 5 to 3 7 per cent If the practitioner decides to supplement the intravenous priming dose of sodium sulfadia ine with insoluble sulfonamide the oral dose approxi mates 4 gm for the first dose (8 tablets each of 0 5 gm) Thereafter the daily maintenance dose is the equivalent of the initial dose given in four divided portions of 2 tablets each (1 gm)

5 For oral control of cholera other experts recommend the inter mediately soluble thalamyd (phthalylsulfacetimide Schering) given orally in the amount of 0 2 gm per kilogram of body weight This requires the average adult weighing 150 lbs to swallow 28 tablets each containing 0 5 gm Thereafter the do e may be decreased to 6 or 9 gm daily (12 to 18 tablets) or 2 or 3 tablets every four hours

6 English investigators have experimented with preparation 6257,

turbances Occasionally patients notice blurring of vision and difficulty in focusing None of these side reactions are serious and all are reversible

CHOLERA

(Asiatic Cholera)

General Principles of Diagnosis and Treatment

With effective use of measures already in the possession of public health authorities epidemics of cholera can be eliminated For the afflicted therapeutic measures of great potential specific efficacy are available

Practical Management

Prophylaxis

1 General measures for the prevention of cholera require vigorous action on the part of public health authorities In addition each householder and physician strives for individual protection through a combination of hygienic and anti infective measures

2 During threatened or actual epidemic of cholera local health authorities are faced with a formidable problem Sources of water supply are pinked with a sufficient amount of potassium permanganate strict isolation is required for the afflicted who preferably are transferred to public institutions contacts and households of known sick are placed out of bounds clothes linen and mattresses used by the afflicted must be destroyed or sterilized and excreta chlorinated

3 In the individual household the following general hygienic measures are introduced to protect members of the family

(a) Screen windows and doors
(b) Use an insecticide such as DDT aerosol bomb (p 4377) to kill flies and other insects
(c) Thoroughly boil water whether used for drinking cooking or washing
(d) Do not use and serve foods that have been handled Rely on canned goods exclusively and boil these before serving
(e) *Insist that every member of the household scrub hands* thoroughly after urination and defecation

4 Give each member of the household and of community prophylactic vaccination with a preparation of V comma U S P (Lilly) (1 cc contains 8 billion killed organisms) For those who have not been previously protected inject an initial dose of 0 5 cc subcutaneously After seven to ten days give a second injection of 1 cc Thereafter deposit a booster dose of 1 cc every six months while the individual continues to live in an area where cholera is endemic or epidemic

5 Contacts who have had previous cholera inoculations within the past six months require only the booster dose of 1 cc on fresh exposure

CHOREA

[St Vitus Dance]

Principles of Diagnosis and Therapy

1 Regard chorea as a cerebral form of rheumatic fever in which encephalitic lesions result from obliterating endarteritis

2 In addition to classical chorea rheumatic encephalitis may produce bizarre neuropsychiatric manifestations including hallucinations phobias panic like episodes delirium increased psychomotor activity restlessness muscle twitchings and convulsions

3 In some instances manifestations of rheumatic encephalitis resemble those of schizophrenia (p 1364) As a further suggestion of the possible identity of the two syndromes evidences of endocarditis were found at autopsy in 6 4 per cent of a group of patients who died in a hospital for mental disease

4 Treat the patient with chorea in the manner of one suffering from classical rheumatic fever (p 4493) Particularly withhold salicylates partially because they have been found to be of no benefit in the treatment of rheumatic encephalitis and chorea and additionally because the delirium that occurs as a manifestation of salicylism confuses the clinical syndrome

CHROMOBLASTOMYCOSIS

[Verrucous Dermatitis]

Principles of Diagnosis and Treatment

1 Chromoblastomycosis is a fungus disease which usually presents only local cutaneous manifestations (Fig 970 p 3315) Only rarely have systemic lesions been observed

2 Diagnosis is established by identification in spreads and cultures from the lesion of the etiologic agents Hormodendrum pedrosi Hormodendrum compactum or Phialophora verrucosa

Practical Management

Immediate Care

1 Attempt surgical excision if lesion can be totally extirpated without producing disturbances of function or excessive scarring

2 Reserve electrocoagulation for destruction of areas not amenable to surgical excision

3 Treat extensive cutaneous lesions that cannot be excised surgically or destroyed by electrocoagulation by iontophoresis using copper sulfate After protecting normal skin areas with petrolatum immerse involved extremity in a bath of 1% copper sulfate Place negative electrode on arm and positive electrode in solution Pass galvanic current of 2 5 ma through bath daily for thirty minutes After nine weeks increase to 10 ma

a sulfonamide containing two parts of sulfathiazole and three parts of formaldehyde This new product with the formula $C_{22}H_{1}O_6N_6S_4$ is not yet commercially available When used it may be prescribed in an initial dose of 10 gm on the first day 4 to 6 gm on the second day 4 gm on the third day 2 gm on the fourth day and 1 gm thereafter for three to seven days until a total of 25 to 30 gm has been administered Following this routine 82 to 85 cholera patients survived recovery occurring within seventy two hours

7 Introduction of aureomycin or chloramphenicol may resolve conflicting opinions concerning sulfonamides and simplify procedure If an intravenous loading dose of aureomycin hydrochloride has been given the patient may then receive maintenance doses approximating 100 mg per kilogram of body weight per day (7 gm or 28 capsules for the average adult weighing 150 lbs) To accomplish this with minimum gastric discomfort 2 capsules are swallowed every few hours with an abundant quantity of milk soup ice cream or fruit juice

8 If there is gastric intolerance to aureomycin substitute chloramphenicol

9 No matter which antibiotic is chosen continue specific therapy *for at least three afebrile days*

10 The use of antibiotics alone is not sufficient to overcome the ravages of cholera Many symptoms of the disease are due to dehydration and salt deficiency The syndrome of pa pin is caused by a barium containing salt which produces paralysis of muscle simulating periodic family paralysis (Amer J Med Sci 214 155 1947) The physician is required to maintain fluid and electrolyte balances by intravenous introduction of saline and plasma particularly if there is considerable vomiting and diarrhea

At the same time fluid loss must be prevented Diarrhea is controlled by deodorized tincture of opium administering 0 5 to 1 cc orally with each evacuation If the stomach is not tolerant dramamine merits trial in doses of 100 mg every three or four hours

As soon as the stomach is tolerant resume oral fluids using boiled water tea soup and boiled milk to tolerance

Continuing Care (Unfavorable Course)

1 With continued difficulty the practitioner sets up a continuous intravenous drip

2 For maintenance of metabolic requirements introduce at least 1 000 cc more fluid than the calculated amount of vomitus and diarrheal excrement For the intravenous fluid use 5% dextrose in saline or distilled water 500 cc of plasma and 500 cc of whole citrated blood

3 For anti infective action inject 2 gm of sodium sulfadiazine or sodium sulfamerazine diluted with 200 cc of physiologic saline and 500 mg of aureomycin hydrochloride

4 Continue the drip alternating blood serum dextrose in saline soluble sulfonamide aureomycin sedative and opiate according to need

observed also in Chinese inhabitants of the United States Cuba and Hawaii (p 1982) The diagnosis is established by identification of ova in stools (Table 191 p 3732)

2 In four patients recently discovered in New York City gentian violet (methylrosaniline chloride) in 1½ hour enteric-coated tablets proved clonorchicidal in doses of 60 to 120 mg given thrice daily for three weeks Chloroquine was found ineffectual

3 Reserve intravenous injections of freshly prepared sodium antimony tartrate (2%) for patients showing symptoms of sufficient severity to warrant the discomforts and hazards of antimony therapy (p 4224) As an initial dose give 60 mg (3 cc of 2% solution) If there are no untoward manifestations double the dose and repeat every second day until a total of 1 3 to 1 8 gm (65 to 90 cc of 2% solution) has been delivered

COCCIDIOIDOMYCOSIS

[Valley Fever Desert Rheumatism San Joaquin Valley Fever Posadas Wernicke Disease Coccidioidal Granuloma]

Principles of Diagnosis and Treatment

1 As the result of intensive training courses in desert country during World War II and of vast increase in motor travel particularly through Southern California there has been a wide dissemination of coccidioidomycosis in the United States Endemic areas of the disease exist in west Texas southern New Mexico southern and central Arizona southwestern Utah southern Nevada and in the valleys of southern California

2 Many who acquired the disease in endemic foci have returned to their homes so that there is no locality in the United States in which coccidioidomycosis may not be encountered The disease merits consideration in the diagnosis of chronic arthropathies (p 2802) and chronic pneumonitis (p 404) In pulmonary infections coccidioidomycosis is especially suspected when there are associated cavitations and calcifications when tubercle bacilli are not demonstrable and most especially when tuberculin and histoplasmin tests are negative (Fig 505 p 2212)

3 The diagnosis of coccidioidomycosis is established by isolation of the fungus from cutaneous lesions and from biopsy of skin or lymph nodes tissue or sputum cultures (Fig 75 D p 486)

4 A presumptive diagnosis may be suggested by noting skin sensitivity to intracutaneous injections of coccidioidin (p 501) obtainable from the Veterans Administration or from Dr John Kessel of The Los Angeles County General Hospital Los Angeles (33) California

Skin sensitivity tests for coccidioidomycosis are carried out in the same manner as tuberculin tests Patients with systemic manifestations are first injected with a 1 1000 dilution and a reading is made at the end of forty eight hours In the presence of a negative response the

4 *Try roentgen radiation on resistant lesions that do not respond* to measures previously outlined

5 Although iodide has been used orally as the saturated solution of potassium iodide (p 4377) and intravenously (1 gm sodium iodide daily) most experts have little confidence in the effect of the preparation The Military Medical Manual of Tropical Medicine published under the auspices of the National Research Council reports that iodides have no effect

6 Systemic and topical applications of sodium sulfamerazine are said to sterilize lesions of chromoblastomycosis Give a priming intravenous injection of 5 gm dissolved in at least 200 cc of normal isotonic saline solution Maintenance oral doses approximate 3 gm daily with equal amounts of bicarbonate of soda Wet dressings of 10% sodium sulfamerazine may be applied to lesions

7 With evidence of systemic invasion inaugurate steps suggested for management of actinomycosis (p 4141)

CIRCULIN

An antibiotic obtained from broth cultures of a mucoid variant of *Bacillus circulans*

Available Product

Circulin is not yet commercially available

Bacterial Spectrum

Circulin active against gram positive and gram negative bacteria and against fungi is bactericidal as well as bacteriostatic Its potency is not appreciably reduced by blood serum

Toxicology

Circulin is hemolytic and extremely toxic It is unsuitable for parenteral administration though it may have possible value in local treatment of bacterial and fungous infections of the skin

Therapeutics

When available circulin may be tried locally in superficial bacterial and fungous infections

CLONORCHIASIS

(Chinese Liver Fluke Infestation)

1 Infestations with Chinese liver flukes are frequently encountered in fish-eating peoples of Japan Korea and China They have been

fibroblasts and the reticulo endothelial system including lymph nodes spleen bone marrow and Kupffer cells of the liver

The collagen diseases appear to be caused by disturbances of the entire me enchymal defense unit They are undoubtedly related to those perversions of the mechanisms of defense now recognized as allergic hypersensitivity reactions (p 4169) Quite likely introduction of alien antigen in the hypersensitive re ults in abnormal activity of defense mechanisms characterized by alterations in serum globulin and mesenchymal tissues The latter react by degeneration and proliferation

The concept of collagen disease has more than academic importance Since Hench and associates have shown regression of collagen dis turbances following administration of corti one and ACTH practi tioners eagerly await adequate supplies of these products in order to translate hypothesis into therapeutic reality

COLON BACILLUS INFECTIONS

Principles of Diagnosis and Therapy

1 E coli a normal inhabitant of the lower intestinal tract gains easy access to the peritoneum and to urinary and biliary pa sages

2 E coli must be considered the primary or a econdary pathogen in every colonic peritoneal biliary or urinary infection

3 E coli is ensitive to aureomycin chloramphenicol sulfonamide and the streptomycins The efficacy of these antibiotics has made obsolete coli vaccine and a long list of urinary anti eptics including acriflavine caprokol formin hexamethylamine hexylre orcinol meth enamine pyridium serenium and urotropin

Practical Management

Prophylaxis

1 Prior to instrumentation of the urinary tract (catheterization cystoscopy) and before any surgical procedure involving peritoneum rectum anus and urinary or biliary pa sages give prophylactic anti biotic therapy aimed at elimination of E coli and allied organisms For optimum protection against the widest range of the bacterial spec trum prescribe aureomycin or chloramphenicol Of the former recom mend doses of 2 gm daily (approximately 25 mg per kilogram of body weight for the average adult weighing 150 lbs) Of chloram phenicol give slightly higher doses approximating 3 gm daily Con tinue maintenance doses of antibiotic for five to seven days before the projected procedure

2 If expense is a factor substitute sulfonamide whose range of bacterial coverage is appreciably less than aureomycin and chloram phenicol and whose toxicity is appreciably more

3 If a soluble sulfonamide is selected give equal parts of sulfadia

test is repeated using 1 100 dilution In the investigation of chronic pneumonitis tests are also made with tuberculin and histoplasmin

Practical Management

Immediate Care

1 Since there is no specific for the treatment of coccidioidomycosis the practitioner is dependent primarily upon general hygienic measures

2 Excise cutaneous manifestations of coccidioidomycosis if possible This failing try roentgen radiation electrocoagulation and ionto phoresis with copper sulfate as described in the management of chromoblastomycosis (p 4287)

3 Treat the patient with chronic pulmonary coccidioidomyco is as if afflicted with chronic tuberculosis Bed rest is mandatory in the presence of systemic manifestations a high caloric diet is ordered (p 671) *vitamin supplementation is advisable particularly with vita mins* A and C the former is given orally in daily doses of 100 000 units while vitamin C is injected intramuscularly as 250 to 500 mg of ascorbic acid transfusions are recommended for those who are anemic immuno transfusion with blood drawn from donors inoculated against coccidioides may be tried as a measure of desperation

4 Inject coccidioidin vaccine starting with an initial intramuscular dose of 0 01 cc of the highest dilution to give a po itive intracutaneous reaction If there is no severe reaction after two or three days inject the same dose intravenously Thereafter twice weekly increase the dose by increments of 0 01 cc until 1 cc of the dilution can be given without significant systemic reaction The next higher dilution is then employed in similar manner until the patient receives 0 3 to 0 5 cc of undiluted vaccine

5 It has been suggested that vaccine therapy be accompanied by intramuscular injections of colloidal copper using 5 cc every fourth day until 10 to 25 injection have been made

6 On an empiric basis oral administration of benzoic acid has been recommended in conjunction with vaccine therapy Every four hours 1 gm *is administered for a week The dose is then increased to* 1 5 *gm* if tolerated Symptoms of benzoic acid poisoning are similar to those of salicylism (p 3834)

7 It has been abundantly shown that the following anti infective agents have no value in the treatment of coccidioidomycosis penicillin streptomycin iodide antimony sulfonamides thymol and gentian violet

COLLAGEN DISEASES

The collagen diseases include rheumatoid arthritis rheumatic fever serum sickness peri arteritis nodosa lupus erythematosus scleroderma dermatomyositis glomerulonephritis malignant hypertension and other syndromes in which alterations are observed in cartilage bone

Continuing Care (Unfavorable Course)

1 With a progressively unfavorable course suspect diminished patient resistance organism insensitivity or local mechanical difficulty

2 To strengthen patient resistance consider plasma infusion or transfusion of whole blood

3 To bacteriologist send specimen of infected urine stool bile or peritoneal exudate Request gram stain for description of predominant organism Test sensitivity of isolated microbes to available antibiotics

4 For evidences of mechanical difficulty consult surgeon or urologist If biliary or urinary calculi congenital anomalies or undrained pockets of pus are demonstrable suggest surgical intervention for their correction

5 Increase dose of antibiotic Raise aureomycin or chloramphenicol to daily quantities approximating 100 mg per kilogram per day (7 gm for average adult weighing 150 pounds)

6 Consider combining antibiotics giving equal parts of aureomycin and chloramphenicol to total 100 mg per kilogram per day (3 5 gm of each for average adult weighing 150 pounds)

7 Consider supplementation of aureomycin and/or chloramphenicol with sulfonamide For intravenous introduction inject loading dose of 2 5 gm each of sodium sulfadiazine and sodium sulfamerazine in at least 200 cc of diluent preferably molar lactate For oral priming dose prescribe 2 to 4 gm each of sulfamerazine and sulfadiazine with 1 teaspoonful of bicarbonate of soda Follow by daily maintenance doses of an amount similar to loading dose divided into 4 equal portions given at six hour intervals

8 If neither aureomycin nor chloramphenicol is tolerated combine sulfonamide with streptomycin as previously detailed

9 Concurrently with sulfonamide or streptomycin start prophylactic doses of antihistamine using 200 mg daily of pyribenzamine or benadryl

10 In the rare instance of organism resistance to commercially available antibiotics apply for polymyxin despite its nephrotoxicity Under supervision inject 25 mg per kilogram of body weight (1 75 gm for average adult weighing 150 pounds) for priming and daily maintenance doses

COLORADO TICK FEVER

(American Mountain Fever Non Exanthematous Tick Fever Tick Fever)

Colorado tick fever is a viremia (Cox) and not a rickettsial disease as previously reported (p 384)

Principles of Diagnosis and Treatment

1 Onset of Colorado tick fever is acute the patient noting the development of symptoms almost to the minute

zine and sulfamerazine with a teaspoonful of bicarbonate of soda Prescribe daily 2 gm of each for four to seven days prior to operation

4 If an insoluble sulfonamide is selected particularly for its effect on intestinal contents prefer sulfathalidine in a priming dose of 3 gm for the average adult weighing 150 pounds Maintain sulfonamide levels in the feces with daily maintenance doses of 3 to 6 gm

5 If the intermediately soluble sulfonamide thalamyd is chosen administer doses comparable to those of sulfathalidine

Immediate Care

1 For treatment of mild urinary infections with acid urine start with mandelic acid Give the adult of average size 3 gm of calcium mandelate 4 times daily Limit fluids to 1000 cc Check urinary acidity with chlorphenol red papers supplied by manufacturer

2 For persistent or more virulent infections whether of urinary passages peritoneum biliary system or colon disregard factor of expense and prescribe aureomycin or chloramphenicol Give a priming dose of 25 to 50 mg per kilogram of body weight per day (2 to 4 gm for the average adult weighing 150 pounds) Approximate the lower dosage with aureomycin and the higher with chloramphenicol Suggest that 2 products be taken every few moments with large quantities of milk ice cream fruit juice soup or tea to prevent gastric irritation

3 Several hours after priming dose begin maintenance doses using a total 24 hour quantity equal to that of the priming dose Divide into four equal portions Give at approximately 6 hour intervals

4 If stomach is intolerant of either antibiotic substitute the other remembering to use chloramphenicol in slightly larger and aureomycin in slightly smaller doses

5 If stomach is intolerant of both make a saline solution of either and instill into rectum Introduce through a funnel attached to inserted catheter Hold buttocks firmly together particularly in infants and children to prevent expulsion

6 If aureomycin and chloramphenicol are not tolerated orally or by rectum inject 100 to 500 mg of aureomycin hydrochloride for intravenous use in diluent of 0 75% sodium carbonate supplied by manufacturer

7 As a less effective and more toxic substitute for aureomycin and chloramphenicol deposit streptomycin intramuscularly Give 1 gm twice or thrice daily depending on severity of infection and patient response

8 Concurrently with streptomycin and for a period of at least two weeks after the last dose prescribe antihistamine prophylactically using 200 mg daily of pyribenzamine or benadryl (p 4211)

Continuing Care (Favorable Course)

1 If symptoms subside and objective evidences of infection abate continue maintenance doses of mandelic acid aureomycin chloramphenicol or streptomycin as above

nous to the nasopharynx especially staphylococci streptococci pneumococci and other antibiotic sensitive bacteria

6 With these concepts for background specific therapy of the common cold may be attempted using antihistamines local bactericides and virucides in preliminary phases and systemic bactericides for prophylaxis and treatment of late purulent complications

7 Useless for prophylaxis or treatment are inhalations or inunctions of highly publicized volatile oils catarrhalis vaccine cold vaccine enterol influenza bacterial vaccine orovax and other respiratory vaccines and vitamins

Practical Management

Immediate Care

1 Attempt to limit spread of infection by cautioning patient to use disposable tissues for nasal secretion to wear a mask of at least three thicknesses of gauze at all times and to control sneezing so that atmosphere is not heavily sprayed with offending virus

2 If possible try to persuade patient to remain in bed during acute phases of illness This precaution limits infectivity reduces complications and shortens convalescence

3 Symptomatic therapy elsewhere outlined may be comforting (p 395) But avoid treatment rhinitis due to overenthusiastic local use of adrenergens and/or bactericides

4 To combat hypersensitivity phenomena in early stages of the common cold prescribe combined antihistamine and adrenergen (p 4212) Available commercial preparations include pyribenzamine ephedrine (12 and 25 mg) benadryl-ephedrine (10 and 50 mg) and histadyl ephedrine (16 and 50 mg) Order a single product after each meal and another at bed time With the last dose give a hypnotic to offset cerebral stimulation by adrenergen In the experience of Brewster of the United States Navy (1949) antihistamine alone given within the first six hours of onset of the common cold resulted in aborted infections in 116 of 156 patients

5 With marked nasal obstruction supplement oral therapy with local adrenergen For decongestant effect suggest an inhaler such as benzedrine tuamine or vonedrine Caution patient not to exceed four or five inhalations daily

For adrenergic decongestant action by instillation prescribe privine hydrochloride in 0 1 or 0 05% solution Caution patient not to exceed three drops in each nostril at each instillation Do not permit more than three or four instillations daily preferably alternating with inhalation of adrenergen

6 For office aerosol therapy dissolve 10 000 units of bacitracin (p 4247) in a solution of chloresium (p 4282) Preferably give two treatments daily Avoid penicillin if possible to prevent sensitization precluding later use of antibiotic when need is greater

2 Initial complaints include chilling generalized aches headache pain in eyes or lumbar regions anorexia nausea vomiting and photophobia

3 Examination reveals elevation of temperature to 102 or 104° F and no other significant findings There is notably no eruption as in Rocky Mountain spotted fever and other rickettsemias

4 Blood counts reveal leukopenia The Weil Felix reactions are completely negative A complement fixation test using mouse brain antigen appears on the ninth to the fourteenth day after onset

5 The initial temperature lasts for approximately forty eight hours There is then a remission of two or three days and a recrudescence for another forty eight to seventy two hours The saddle back temperature record is quite characteristic

6 In convalescence there is prolonged asthenia Patients develop a lasting immunity Complications and fatalities are unknown

7 Prophylaxis of Colorado tick fever is best accomplished by avoiding the vector which alone to the best of present knowledge transmits the disease

8 A vaccine of chick embryo adapted virus is presently under experimental investigation Further information may be obtained from Lederle Laboratories

9 Of the antibiotics only aureomycin and chloramphenicol appear likely to influence the disease in any way Because of the benign character of the affliction only symptomatic therapy appears necessary

COMMON COLD

(Upper Respiratory Infection)

Principles of Diagnosis and Therapy

1 While the specific virus of the common cold continues to be elusive many empiric ob ervations justify abandonment of the previous therapeutic policy of defeatism (p 391)

2 In addition to the specific virus upper respiratory infections are produced by a wide variety of antibiotic sensitive organisms including staphylococci streptococci pneumococci Klebsiella etc

3 Granting that the upper respiratory infection most often is due to antibiotic resistant cold virus elimination of antibiotic sensitive organisms may assist the tissues in their defense mechanisms in the manner in which penicillin and aureomycin supplement amebacides in amebiasis (p 4183)

4 In the early stages of many microbic invasions of the upper respiratory passages symptoms resembling acute histamine type allergic hypersensitivity reactions are encountered These simulate the vasomotor rhinitis of pollinosis (hay fever) (p 2097)

5 Later phases of upper respiratory infections feature secondary complications resulting from tissue invasion by micro organisms indige

CONTACT ATOPY

[Contact Dermatitis Eczema Occupational Dermatitis Dermatitis Venenata]

Earliest recognition of dermatitis venenata occurred in the sensitized who developed eruptions when exposed to poison ivy oak or sumac More recently it has become apparent that an infinitely larger number of individuals suffer from contactual atopies from cosmetics and chemicals used occupationally (Fig 982 p 3331 and p 3330)

Principles of Diagnosis and Treatment

1 Identify offending contactual substance by history and process of elimination Patch tests may occasionally be of value (p 556)
2 Eliminate contactual substance if nonessential
3 In the case of cosmetics substitute allergen free products (Almay Marcelle)
4 In occupational dermatitis try to guard against actual contact with offending substance If impossible suggest change of position
5 In the case of poison ivy oak or sumac desensitize with rhus extracts Inject intramuscularly 1 cc and repeat dose after interval of two weeks Official poison ivy extracts are available from Abbott Laboratories Hollister Stier Lederle Mulford Parke Davis and Pitman Moore Poison Oak Extract from Hollister Stier Lederle and Pitman Moore Poison Sumac from Mulford
6 For palliation in all instances prescribe antihistamines as in serum sickness (p 4519) Supplement with adrenergens if necessary Use intravenous procaine as a desperation remedy (p 4567)

CORTISONE CORTONE

[See Adrenal Cortical Extracts]

DDT

[Chlorinated Diphenyl Ether]

DDT is the most valuable insecticide used by the United States Army *It has revolutionized the problem of insect control All other preparations currently under trial require comparison with DDT* Hence it is important for the practitioner to be aware of its properties and hazards

Chemically DDT is 2 2 bis (*p* chlorophenyl) 1 1 1 trichloroethane) It is a white powder prepared synthetically

Available Products

DDT Powder (100%) for preparation of dusts suspensions emulsions and solutions

DDT Louse Powder (10% with 90% pyrophyllite) For individual delousing

Continuing Care (Unfavorable Course)

1 If combined adrenergic antihistamine bactericidal therapy is unsuccessful if onset of respiratory infection is accompanied by temperature elevations in excess of 102° F if there is chilling actual chills or excessive prostration or toxemia if patient is an infant an aged person or one suffering from chronic illnesses of whatever type start probatory virucidal therapy with aureomycin or chloramphenicol provided that the expense is not excessive Order a loading dose of 25 to 50 mg per kilogram of body weight (1 75 to 3 5 gm for average adult weighing 150 pounds) Approximate the lower concentration with aureomycin and the higher for chloramphenicol Suggest that 2 products be taken every few minutes with milk fruit juice tea soup ice cream or cream cheese to minimize gastric irritation

2 Continue oral antihistamine adrenergen and intranasal adrenergen

3 Maintain levels of virucide by giving daily maintenance doses of aureomycin or chloramphenicol equal to priming dose Start four to six hours after priming dose has been completed Divide total daily quantity into 4 equal portions given at six hour intervals

4 With initiation of virucidal therapy discontinue aerosolization with bacitracin

5 Despite pressure avoid local or systemic use of sulfonamides penicillin silver salts mercurials iodides etc Sulfonamide toxicity and hypersensitivity phenomena are particularly hazardous (p 4179)

Continuing Care (Progressively Unfavorable Course)

1 With onset of purulent complications discontinue oral combination of adrenergen antihistamine

2 Continue intranasal adrenergen adding 0 25 to 1% cocaine if necessary to drain accessory nasal sinuses

3 Continue maintenance doses of aureomycin or chloramphenicol

4 Supplement aureomycin or chloramphenicol with parenteral penicillin Introduce intramuscularly 600 000 units of procaine penicillin G in aqueous suspension for priming dose Repeat at eight, twelve or twenty four hour intervals depending on course of events

5 Start straight antihistamine orally Give 200 mg daily of pyribenzamine or benadryl Continue for at least two weeks after last dose of antibiotic to prevent or mitigate hypersensitivity reactions (p 4167)

CONJUNCTIVITIS

See Inclusion Conjunctivitis Koch Weeks Conjunctivitis Epidemic Keratoconjunctivitis Vernal Conjunctivitis and Morax Axenfeld Conjunctivitis

critical rise falls by crisis On the third day there is often a partial defervescence giving a saddle back appearance to the chart.

6 On the third to fifth day a maculopapular or scarlatiniform rash appears on the trunk and spreads to extremities and face Occasionally the eruption is petechial

7 Physical examination reveals only the rash and lymphadenopathy

8 The viremia is demonstrable by special technics Many different strains may be isolated partially accounting for protean clinical manifestations

9 Convalescence is prolonged due to persistent asthenia Specific virus neutralizing bodies are demonstrable

Practical Management

Prophylaxis

1 Vector control employing insecticides (p 4373) for individual protection

2 Injection of mouse adapted vaccine virus prepared by United States Army Medical Corps has proven stable safe and efficient in human volunteers

Immediate Care

1 Isolation

2 Symptomatic relief (p 68)

3 Probatory anti infective therapy with chloramphenicol or aureomycin

DERMATITIS HERPETIFORMIS

[Duhring s Disease]

Although it has been reported that sulfapyridine is of value in the treatment of dermatitis herpetiformis (Fig 945 p 3241 and p 3371) therapeutic trials with le s toxic aureomycin and chloramphenicol appear distinctly warranted

Those who use sulfapyridine prescribe 1 gm thrice daily for the first day and 0 5 gm thrice daily thereafter Because of the unknown etiology of the disease and the suspicion that it may be a manifestation of allergic hypersen itivity antibiotic therapy is best supplemented with antihistamine (p 4212)

DERMATOMYOSITIS

Principles of Diagnosis and Therapy

1 Regard dermatomyositis (p 3373) as a manifestation of chronic tuberculin type hyper ensitivity (p 4168) with predominant cutaneous

DDT Larvicide Powder (10% in talc) Dilute with four parts of dust for mosquito larvicide Use undiluted as roach powder

DDT Sprays (1 to 5% solution) For surface deposit against flies mosquitoes roaches bedbugs and ants

DDT Aerosol Spray Bomb 2% pyrethrum (of 20% extract) 3% DDT, 5% cyclohexanone 5% hydrocarbon oil and 85% Freon 12 Dispensed in metal or in bomb For home use to kill mosquitoes flies etc Spray for four seconds for each 1000 cubic feet

Action on Insects DDT apparently enters through the tarsi It kills the animal by excitation and paralysis of the central nervous system When insects are sprayed they fly around in erratic circles for ten to twenty minutes then fall to the ground apparently paralyzed and die several hours later

Human Toxicity DDT appears to have minimum toxicity for the human being whether used as spray dusting powder or as a food contaminant In a few human instances of poisoning where large doses were taken mistakenly for baking powder giddiness and weakness developed in one to two and a half hours Additional symptoms included nausea vomiting anxiety stiffness pains in the jaws and soreness of the throat for several days All patients recovered within forty eight hours though one instance of a fatal poisoning in a child was reported from a dose that approximated 150 mg per kilo

Insecticidal Activity DDT (Table p 4373) is of unparalleled value as an insecticide As such it has the property of preventing dissemination of disease either endemically or epidemically when the microbic pathogen is vector borne

DDT is toxic for mosquitoes and their larvae for mites chiggers lice tick fleas housefiie biting flies cockroaches gnats bedbugs and ants Its use in scabies is disappointing but fortunately other scabicides are currently available (p 4513)

DENGUE AND DENGUE LIKE FEVERS

[Breakbone Fever Dandy Fever Bouquet Fever Giraffe Fever Polka Fever van der Scheer Five Day Fever Panama Six Day Fever Seven Day Fever of India]

General Principles of Diagnosis and Therapy

1 Dengue and dengue like fevers are viremias the former are mosquito borne (Aedes aegyptis) in the latter the sandfly is the vector (p 406)

2 Epidemics have a high attack rate but negligible mortality (3 per 10 000)

3 The incubation period may vary between two and one half and eighteen days but the average is five to eight days

4 The onset is usually acute with rise of temperature chilliness multiple aches and pains photophobia dysuria epi taxis constipation and marked prostration

5 Fever usually persists for five or six days and then *after a pre*

NEOPLASMS OF OROPHARYNX

Practical Management

1 During routine examination look for cysts and neoplasms (Table 120 p 1714 p 1712–1719 Figs 374–382 pp 1713–1719)
2 Get blood for serologic test for malignancy (p 4431)
3 Pefer to oral surgeon for opinion and removal of specimen for biopsy
4 Consider surgical excision and/or roentgen therapy

NEOPLASMS OF ESOPHAGUS

Practical Management

1 Question the patient as to dysphagia (p 1722)
2 Obtain blood for serologic tests for malignancy (p 4431)
3 Order contrast roentgenograms using thick barium mixture Exclude non neoplastic disturbances of esophagus (Fig 383 p 1721 Fig 385–391 pp 1725–1737)
4 Note characteristic mouse eaten deformity of malignancy (Fig 392 p 1739)
5 Refer patient to specialist for esophagoscopy and to obtain speci men for biopsy
6 Consider radical surgery

NEOPLASMS OF STOMACH

Practical Management

1 Palpate for masses in the epigastrium (p 1814)
2 Examine daily stool specimens for evidences of occult bleeding (p 1843)
3 Inquire into history of anorexia (p 1779) or dyspepsia (p 1770)
4 Obtain gastric contents Note absence of free hydrochloric acid Send specimen to clinical pathologist for cytodiagnosis using Papani colaou stain
5 Get blood for serodiagnosis of malignancy (p 4431)
6 If possible obtain electrogastrogram (p 4431)
7 Pefer to specialist for gastroscopy
8 Pefer to roentgenologist for contrast x rays (Figs 408–410 pp 1815–1818)
9 On suspicion of neoplasm presumably malignant consider laparotomy and radical gastrectomy

NEOPLASMS OF COLON AND RECTUM

Practical Management

1 Palpate abdomen carefully at each physical examination Remember that the normal colon is palpable especially in lean indi viduals and particularly when there is associated spasmosis Neverthe less exclude possibility of neoplasm on slightest su picion particularly

lesions (Fig 988 p 3373) and accompanying widespread systemic disturbances (p 4166)

2 Quite possibly the offending allergen is bacterial and more than likely streptococcal

3 Treat as acute lupus erythematosus recalling favorable therapeutic result with ACTH

4 Oral administration of 2 gm of para aminobenzoic acid (PABA) every two hours night and day for several months greatly improved a small group of patients at the University Hospital of Michigan

DERMATOPHYTOSIS

[See Fungus Infections]

DIASONE

Diasone (disodium formaldehyde sulfoxylate diamino-diphenyl sulfone) is prepared as a light yellow stable powder

Available Products

Not yet commercially released diasone is put up *in capsules or* tablets of 0 3 gm with 10% sodium bicarbonate for investigation only

Administration

Doses of diasone start with 0 3 gm daily increased to 0 3 gm thrice daily and continued for two months After a rest period of two weeks the course may be repeated Frequent blood counts and urinalyses are required for early detection of anemia leukopenia thrombocytopenia and hematuria

Pharmacology and Toxicology

[See Sulfones]

DIGESTIVE SYSTEM NEOPLASMS OF

Neoplasms of the digestive tract constitute a daily challenge to the practitioner Tumors of the oropharynx are clearly visible to patient dentist and physician lesions of stomach and colon may be palpable long before subjective symptoms arise and growths of rectum and sigmoid may be palpated or recognized by proctoscopy and sigmoidoscopy

The merest suspicion of a positive finding suffices for reference to the specialist for contrast roentgenography esophagoscopy gastroscopy electrogastrography cytologic examination of direct spreads of gastric contents intestinal mucus or feces by the method of Papanicolaou and all else failing consideration of exploratory operation

2 For preparation of choice select diphtheria toxoid (alum precipitated) tetanus toxoid (alum precipitated) pertussis vaccine combined N N R (Parke Davis Squibb Wyeth Lederle National Drug and Sharp & Dohme) Inject 0 5 cc intramuscularly Repeat twice at intervals of four to six weeks to total 3 injections or 1 5 cc

If patient has had pertussis substitute diphtheria toxoid (alum precipitated) tetanus toxoid (alum precipitated) U S P (Lederle Lilly National Drug Parke Davis Pitman Moore Sharp & Dohme Squibb and Wyeth)

3 For stimulating or booster dose inject intramuscularly a single deposit of 0 5 cc If there is direct exposure to diphtheria substitute 0 5 to 1 cc diphtheria toxoid (alum precipitated) U S P (Lederle Lilly National Drug Parke Davis Sharp & Dohme Squibb Wyeth)

4 Local reactions to triple immunization are ordinarily mild If there is significant local pain or swelling apply ice bag or wet dressing If there are constitutional symptoms give acetylsalicylic acid in capsules or tablets containing 0 3 gm Repeat at three or four hour intervals if needed

5 To the hypersensitive give concurrent prophylactic antihistamine in daily do es of 200 mg of pyribenzamine or benadryl Continue for two weeks after last immunization

6 Obsolete are plain diphtheria toxoid (anatoxin Ramon diphtheria anatoxin) U S P and diphtheria toxin antitoxin mixture N N R

Immediate Care

1 Inaugurate general measures required for care of infected patient (p 67)

2 Notify health authorities

3 Inject intramuscularly 5 cc of 1% benadryl for prophylaxis against hypersensitivity reactions (p 4168)

4 Inject intramuscularly 600 000 units of crystalline procaine penicillin G with 200 000 units of crystalline potassium penicillin G in aqueous suspension

5 Inquire into personal or familial history of hypersensitivity Make intracutaneous and ophthalmic tests for sensitivity to horse serum (p 555)

6 With negative sensitivity (p 4190) deposit intramuscularly 50 000 to 100 000 units of diphtheria antitoxin U S P (Cutter Lederle Lilly National Drug Parke Davis Pitman Moore Squibb Wyeth)

7 With definite hypersensitivity administer diphtheria antitoxin by the method of desensitization elsewhere described (p 4191)

8 Concurrently with antitoxin and antibiotic give oral doses of antihistamine approximating 200 mg daily of pyribenzamine or benadryl

9 Take throat cultures of contacts in school industry and household for detection of carriers Make Schick test simultaneously (Fig 43 p 302)

10 Give booster do es of diphtheria toxoid alum precipitated to contacts previously immunized and to Schick negative reactors

if bowel is palpable in an isolated portion and previous records contain no note of this finding

2 Question patient concerning changes in bowel habits whether on the side of diarrhea (p 1840) or constipation

3 Obtain stools daily for at least three days and examine for occult blood (p 1843)

4 Consider differential diagnosis of swellings or tumors in right lower quadrant (p 1886) left lower quadrant (p 1870) epigastrium (p 1814), left upper quadrant (p 1849) and right upper quadrant (p 1957)

5 At each abdominal examination complete survey by rectal palpation Make this examination by bimanual method using the abdominal hand to press the viscera against inserted finger

6 Examine fecal specimen on finger cot or glove for occult blood (p 4384)

7 Obtain blood for serodiagnosis of malignancy (p 4431)

8 On slight suspicion insert proctoscope and sigmoidoscope in attempt to visualize lesion If a growth or ulceration is observed get a surface biopsy and send specimen to clinical pathologist for Papanicolaou stain

9 On suspicion order or perform contrast roentgenography by barium meal and barium enema (Figs 427 and 428 p 1889 Figs 429 and 430 p 1890)

10 Check x ray findings with specialist roentgenologist

11 Check sigmoidoscopic findings with proctologist or surgeon

12 On suspicion of a neoplasm in an area not visible to proctoscopy and sigmoidoscopy consider exploratory laparotomy

DIPHTHERIA

Principles of Diagnosis and Therapy

1 With compulsory immunization diphtheria can be eliminated

2 Effective artificial active immunization can be induced by injection of diphtheria toxoid

3 Despite availability of potent antitoxin and of antibiotics of considerable bacteriostatic and bactericidal potential active treatment of diphtheria is less successful than prevention

4 Diphtheria is a grave and treacherous disease whose late complications may follow seemingly mild infections In consequence treatment must be prompt and persistent using massive doses of available anti infective agents

Practical Management

Prophylaxis

1 Advise active immunization of all infants preferably between sixth and twelfth months of life and of Schick positive adults (Fig 43 p 302)

DIURETICS

Mercurials continue to dominate the important field of diuretic activity The accompanying chart and notes summarize and supplement previous considerations (pp 2257–2262)

MERCURIAL DIURETICS

Preparation	Council Accepted Commercial Preparations
Meralluride Sodium N N R.	Mercuhydrin sodium solution (Lakeside) ampuls of 1 and 2 cc (each cc equals 119 mg of meralluride and 13 mg of theophylline intramuscular dose 0 5 to 2 cc Tablets with ascorbic acid each containing meralluride 60 mg and ascorbic acid 100 mg for oral use give 1 to 2 tablets daily for maintenance and 3 to 5 tablets for active diuresis
Mercuhydrin	See Meralluride Sodium.
Mercurophylline Injection U S P	Mercuzanthin (Campbell) Ampuls of 1 and 2 cc (each cc contains 37 to 42% of mercury equivalent and theophylline equivalent of 93 to 107%) intramuscular dose 0 5 to 2 cc Mercuzanthin enteric coated tablets each representing 0 74 cc of mercurophylline injection oral dose 3 to 5 tablets daily for one or two successive days or 5 tablets after breakfast once a week
Mercuzanthin	See Mercurophylline Injection
Mersalyl and Theophylline U S P	Salyrgan Theophylline Solution (Winthrop) ampuls of 1 and 2 cc intramuscular dose 0 5 to 2 cc Enteric coated tablets containing 80 mg Mersalyl and 40 mg theophylline oral dose 3 to 5 daily for one or two successive days or 5 tablets after breakfast once weekly
Salyrgan Theophylline	See Mersalyl Theophylline
Thiomerin N N R	Thiomerin (Campbell) vials containing 10 and 20 cc for subcutaneous injection dose 0 5 to 2 cc

1 Establishment of the dry weight is the most accurate yardstick for determination of indications for use of diuretics and for estimating their efficiency It is not necessary to measure intake of fluid and output of urine

2 Mercurials increase sodium as well as water loss Therefore do not limit sodium intake lest the patient after diuresis evince manifestations of hypochloremia (p 732) or hyponatremia (p 729) requiring addition of salt to the dietary intake

3 Among variables requiring consideration before use of diuretics are concurrent administrations of opium and opium like synthetics and of digitalis bodies Opiates their derivatives and substitutes are antidiuretic The edematous patient concurrently taking any of these preparations may experience a more favorable diuretic response if analgesic is discontinued The edematous digitalized patient given a

11 Consider passive immunization of Schick positive reactors If exposure has been heavy and there are no evidences of hypersensitivity to horse serum inject intramuscularly 5 000 to 10 000 units of diphtheria antitoxin If contact is skin sensitive or has a history of allergy protect with intramuscular deposit of 300 000 to 600 000 units of crystalline procaine penicillin G in aqueous suspension

12 Treat carriers with lozenges containing 10 000 units of penicillin or preferably give three daily intramuscular deposits of 600 000 units of crystalline procaine penicillin G

Continuing Care (Favorable Course)

1 Continue maintenance doses of diphtheria antitoxin using 20 000 to 40 000 units intramuscularly once or twice daily as indicated

2 Continue deposits of penicillin using 300 000 to 600 000 units of procaine penicillin G in aqueous suspension once or twice daily as indicated

3 Continue antihistamine for at least two weeks beyond last dose of antibiotic or heterologous antiserum

4 Maintain bed rest for at least two or three weeks after all evidences of disease have disappeared If possible obtain an electrocardiogram to supplement physical examination before permitting ambulation Particularly exert precautions with persistent tachycardia recent appearance of cardiac murmurs or irregularities or electrocardiographic deviations from the norm

5 Avoid administration of digitalis unless there are clear evidences of backward failure (p 858)

Continuing Care (Unfavorable Course)

1 If disease is hyperacute accompanied by extreme prostration or persistent set up intravenous drip Maintain a rate no faster than 30 drops per minute so as not to overload the vulnerable circulation Introduce first 5 cc of 1% benadryl follow with 50 000 to 100 000 units of diphtheria antitoxin keeping a syringeful of 1 10 000 epinephrine hydrochloride at hand for intravenous introduction if hypersensitivity manifestations are encountered After introduction of antihistamine and heterologous antiserum dissolve 500 000 to 1 000 000 units of crystalline potassium penicillin G in 200 to 500 cc of physiologic saline Maintain drip with antibiotic solution until it is again time to re introduce maintenance doses of antihistamine and antitoxin

2 On slightest suspicion of laryngeal involvement prepare tracheotomy set (p 3958) Preferably alert laryngologist or consultant surgeon for performance of procedure if indicated

3 For supplementation of penicillin consider streptomycin and aureomycin The latter proved successful in a single instance of diphtheria peritonitis and streptomycin was reported by the Council on Pharmacy and Chemistry to be occasionally effective as an antibacterial but not as an antitoxic agent Neither streptomycin nor aureomycin however approximates in effectiveness the combination of diphtheria antitoxin with penicillin

Principles of Diagnosis and Therapy

1 Avoid drugs which frequently cause toxicoderms (p 3339)

2 Eliminate non essential drugs suspected of producing hyper sensitivity

3 If sensitizing drug is essential as in the case of an antibiotic substitute a preparation of similar action but one that is less allergenic (penicillin for sulfonamide aureomycin or chloramphenicol for peni cillin etc)

4 If it is necessary to continue or resume sensitizing drug as in the case of antibiotics try the brand of another manufacturer Give anti histamine concurrently for prophylaxis as well as palliation

5 If hypersensitivity symptoms persist after elimination of offending drug give antihistamine orally and parenterally as in serum sickness (p 4519) Supplement with adrenergen if necessary Add intravenous procaine in situations of desperation (p 4567)

ECHINOCOCCOSIS

[Hydatid Disease Cestodiasis]

Tapeworms which commonly infest man are Taenia saginata (beef) T solium (pork) Echinococcus granulo is (hydatid worm) Hymenolepis nana (dwarf tapeworm) and Diphyllobothrium latum (fish)

Intra intestinal infestations with these invaders are controlled by use *of anthelmintics (p 4561) Extra inte tinal lesions particularly hydatid* cysts produced by echinococcus and cysticerci are not amenable to medical therapy and require surgical interference

Attempts at operative removal or marsupialization of sacs are all that can be currently offered The Chief of the Division of Tropical Diseases of the National Institute of Health Bethesda Maryland asks to be notified in advance of operation so that arrangements can be made to freeze the intact sterile specimen for antigen production

ENCEPHALITIS (ENCEPHALOPATHY) OF POST INFECTIOUS OR POST VACCINAL ORIGIN

General Principles of Diagnosis and Therapy

1 Encephalitis or more properly encephalopathy may follow infec tious diseases such as measles chickenpox smallpox influenza lym phogranuloma venereum herpes simplex rubella mumps and pertussis (p 445)

2 Encephalopathies also may be sequels of vaccination with small pox or rabies virus

3 Most likely these abacterial inflammations result from chronic tuberculin type allergic hypersensitivity (p 4169)

diuretic may suffer an acute attack of digitalis poisoning at the time of diuresis To avoid this discontinue digitalis before giving the diuretic if possible and remove digitalis containing fluid by mechanical aspiration of pleural or peritoneal cavities

4 Supplement mercurial therapy with acid producing ammonium chloride Prescribe 1 to 1 5 gm of ammonium chloride in enteric coated tablets 4 times daily for three to four consecutive days

5 If there is weight increase in excess of 5 pounds over dry weight despite ammonium chloride prescribe 3 to 5 tablets of mercuhydrin with ascorbic acid mercuzanthin or salyrgan theophylline

6 If oral therapy is unsuccessful or inadvisable inject thiomerin subcutaneously or mercuhydrin mercuzanthin or salyrgan theophylline intramuscularly using 0 5 to 2 cc depending on the need and patient response

7 Observe that thiomerin is available for subcutaneous injection In the rare instance when the physician cannot get to the patient at frequent intervals thiomerin may be injected under his supervision by a registered nurse or a member of the family

8 The frequent occurrence of severe reactions following intravenous injection some of which have been fatal should result in a ban on this route of administration Intramuscular and subcutaneous injections are as efficacious and they are free from most hazards

9 When diuresis has resulted in an approximation of dry weight try to maintain the low weight with oral administration of commercially available mercurials Give 3 to 5 tablets once every few days depending on changes in body weight or prescribe 1 to 2 tablets daily for several successive days as needed

10 During mercurial therapy examine urine weekly for evidence of significant albuminuria or hematuria Resume mercurial administration as soon as specimen is clear

DRACONTIASIS

[See Filariasis]

DRUG ALLERGY

[Dermatitis Medicamentosa]

Drug allergies (pp 549 and 3335 Fig 983 p 3333) occur very frequently in routine clinical practice Therapeutic objectives in the management of this type of allergic hypersensitivity include elimination of non essential sensitizing agents substitution of less sensitizing product for an essential drug palliation and prophylaxis with adrenergens and antihistamines

disturbances of the type seen in paralysis agitans These are associated with vegetative manifestations such as sialorrhea dacryorrhea and seborrhea Additionally there are psychotic manife tations particularly depressions

8 The diagnosis is established by clinical manifestations during an epidemic and by virus neutralization tests on blood taken during the height of the disease and in convalescence

9 As yet there is no specific for prevention or cure of epidemic encephalitis For lack of some better specific patients may be given injections of Lederle s encephalitis vaccine (herpes F strain) a 10% rabbit brain suspension of virulent neurotropic virus inactivated by formaldehyde One cubic centimeter is injected intramuscularly or subcutaneously daily for two days Then 2 cc are given daily for four days and 3 cc for seven to ten days Thereafter 4 cc are deposited twice a week until a total of 100 cc has been administered

In chronic encephalitis 1 cc is given daily for two days 2 cc daily for three days and 4 cc twice a week for as long as is necessary with rest periods of one to two months each year

10 For desperation antibiotic therapy large doses of aureomycin or chloramphenicol (100 mg per kilogram of body weight per day) may be tried for possible virucidal activity

ENCEPHALITIS EQUINE

General Principles of Diagnosis and Therapy

1 Eastern and western types of equine encephalitis are specific viral infections which produce non suppurative encephalomyelomeningitis (p 442)

2 Occurrence of the disease in late summer suggests a mosquito vector (p 451)

3 Attempt prophylaxis by mosquito repellents and insecticides (p 4373) and by injections of commercially available (Lederle) formalized chick embryo vaccine first employed for horses Give 2 injections each of 1 cc subcutaneously at intervals of one week

4 Successful serum therapy has been reported with a hyperimmune rabbit preparation and with intramuscular injections of gamma globulin using doses of 10 cc daily for seven days

5 Because of the mortality and morbidity of the disease undertake probatory anti infective therapy with aureomycin and chloramphenicol approximating 100 mg per kilogram for priming and daily maintenance do es (28 capsules daily for adult weighing 150 pounds)

6 If the patient is unable to swallow or has gastric intolerance inject intravenously 500 mg of aureomycin hydrochloride in the supplied diluent of 0 75% sodium carbonate Repeat every 6 8 or 12 hours according to severity of attack and patient respon e

4 While the complication of encephalopathy is not often encountered its con equences are so grave that use of antihistamine is warranted throughout the course of any infectious disease capable of producing it as well as concurrently with administration of virus vaccines

5 For prophylaxis give 200 mg daily of pyribenzamine or benadryl during infection or with administration of vaccine Continue antihistamine for at least two weeks after infection is terminated or last do e of vaccine has been administered

6 For active treatment once evidences of encephalopathy have developed use massive doses up to 800 mg daily of pyribenzamine or benadryl Additionally give parenteral injections of 5 cc of 1% benadryl twice or thrice daily

7 Avoid anti infective agents during course of encephalopathy Particularly refrain from administration of hyperallergenic preparations such as sulfonamides and streptomycins

ENCEPHALITIS EPIDEMIC

[Encephalitis Lethargica Sleeping Sickness Von Economo s Di ea e]

General Principles of Diagnosis and Therapy

1 Epidemic encephalitis is a non suppurative encephalomyelo meningitis of viral origin (p 442) Unlike most other allied disturbances it occurs chiefly in the winter and early spring months suggesting that its spread is not dependent on insect vectors

2 Epidemic encephalitis manifests itself in the early stages by a variety of complicated syndromes The two best defined are the somnolent ophthalmoplegic and the irritative hyperkinetic

3 The somnolent-ophthalmoplegic type of epidemic encephalitis is characterized by a brief initial stage with fever meningeal irritation drowsiness and ocular paralyses

4 The irritative hyperkinetic type is initiated by fever and excitement followed by choreiform movements and myoclonic contractions

5 Other early types of the disease are the psychotic with manifestations ranging from simple mental impairment to simulations of general paresis or schizophrenia the poliomyelitic with lower motor neurone paralyses and involvement of po terior root ganglia tabetic with ataxia epilepto maniacal cataleptic amyostatic akinetic with apathy rigidity akinesia amimia slow motion and tremor and fulminating from which the patient succumbs within a few hours

6 No matter what the nature of the initial stage the second stage of pseudo psychoneurosis which may persist for months or years is characterized by the subjective symptoms of headache insomnia irritability dizziness and fatigue

7 The third or chronic stage may immediately follow the first phase or it may not become manifest until years after It consists of motor

4 Prophylaxis is best accomplished during an outbreak by liberal use of insecticides and insect repellents (p 4373)

5 A vaccine prepared from formalin inactivated or irradiated chick embryo cultures may be obtained from U S Public Health Service to whom inquiries should be addressed

6 The infected patient requires hospitalization and institution of measures suggested for nonspecific treatment of contagious disease (pp 68-73)

7 For active treatment commercially available encephalitis vaccine herpes F strain (Lederle) may be given intramuscularly in do es of 1 cc daily for two days 2 cc daily for four days 3 cc daily for seven to ten days and 4 cc twice weekly to total 100 cc

8 In the absence of specific information chloramphenicol or aureomycin is suggested for probatory anti infective therapy Order initial priming and daily maintenance doses of 100 mg per kilogram (7 gm for the average adult weighing 150 pounds) If there is no response to the chosen antibiotic try the opposite number in the same dose or combine both products

ENCEPHALOMYOCARDITIS

[Three Day Fever of Manila]

Encephalomyocarditis is an epidemic viremia characterized by sud den on et of fever with headache chill coma stiffne s of the neck injection of the pharynx and meningeal manifestations The blood shows leukopenia and lymphocytosis and the cerebrospinal fluid reveals a pleocytosis up to 220 cells with 21 to 95% lymphocytes

Recovery is prompt on the third or fourth day Despite marked cardiac lesions in experimentally infected animals none of a large group of American soldiers afflicted during an epidemic while stationed on the Philippine Islands experienced any complications or sequels

The blood serum of convalescents exhibits neutralization of 100 to 160 lethal doses of the specific virus of encephalomyocarditis and is protective against several thousand lethal do es in animals Treatment however is wholly symptomatic

ENDOCARDITIS ATYPICAL VERRUCOUS

[Libman Sacks Syndrome Visceral Angiitis]

Principles of Diagnosis and Treatment

1 Atypical verrucou endocarditis like rheumatic fever and rheuma toid arthritis (p 4502) is best considered a chronic tuberculin type hypersensitivity probably resulting from an allergic response to bac terial and/or drug antigen (p 4169)

ENCEPHALITIS JAPANESE B

[Australian X Disease]

Principles of Diagnosis and Therapy

1 Japanese B encephalitis is one of many non suppurative encephalo myelomeningitides (p 442) An epidemic on the island of Okinawa in 1945 afforded opportunity for study of the disease as it affected natives and American military personnel

2 Common clinical manifestations in those who gave serologic evidences of having been afflicted with the infection included drowsi ness lethargy confusion disorientation semi coma coma fever rigidity of neck and spine leukocytosis and spinal fluid pleocytosis

3 An appreciable amount of virus neutralizing antibody is demon strable in the afflicted as early as three days after onset of symptoms Thereafter there is a constant increase in the amount of neutralizing antibody Complement fixation tests also are reliable in diagnosis though the appearance of the reaction may be delayed as long as five weeks

4 Neutralizing antibody is present in 90 per cent of adult natives suggesting that the disease is endemic on the island Neutralizing anti bodies also are found in Okinawa horses goats and cows

5 Although the majority of serologically proven military cases occurred in the extreme northern part of Okinawa where mosquito control was inadequate the predominant mosquito of the island (culex quinquifasciatus) is not a carrier of the disease

6 A vaccine administered to 60 000 to 70 000 of the military per sonnel stationed in the northern portion of the island in close proximity to civilian foci of infection proved completely protective While Japa nese B encephalitis vaccine is not commercially available it may be procured through application to the United States Army Medical Corps

7 For active treatment probatory trial of aureomycin and chloram phenicol merits consideration in view of the demonstrable virucidal properties of these antibiotics

ENCEPHALITIS ST LOUIS

General Principles of Diagnosis and Therapy

1 St Louis encephalitis is one of many varieties of nonsuppurative encephalomyelomeningitis (p 442) of specific viral origin

2 Its clinical manifestations are not specific The diagnosis is estab lished epidemiologically and serologically (p 457)

3 The virus is probably insect borne The most likely vector is the mosquito although the disease occurs most frequently *in summer* and early fall

stitution Ave Washington D C for ACTH to Dr John R Mote Armour and Co Chicago Illinois Meantime make clinical trials of artisone (Wyeth) and percorten (Ciba) purchaseable in the open market In the use of the latter inject 1 cc intramuscularly (equivalent to 5 mg desoxycorticosterone) followed within five minutes by intra venous introduction of 10 cc of 10% ascorbic acid (1 gm) Unless prompt and dramatic improvement is noted with artisone and per corten—ascorbic acid abandon therapy after three or four consecutive daily injections

9 In the presence of suspected bacterial allergen institute anti biotic therapy with hypo allergenic anti infective agents such as aureo mycin and chloramphenicol Supplement with penicillin if there is no skin sensitivity to the latter

ENDOCARDITIS SUBACUTE BACTERIAL

(Endocarditis Lenta)

Principles of Diagnosis and Therapy

1 Subacute bacterial endocarditis is a bacteremia in which the invading organism localizes on damaged endothelium usually a heart valve deformed as the result of rheumatic fever (p 1021)

2 The diagnosis is made tentatively by the syndrome of prolonged fever cardiac murmurs and characteristic cutaneous lesions (petechiae Osler nodes and Janeway lesions p 1023 and Fig 224 p 1022)

3 The diagnosis is established definitively by blood culture Once identified the pathogen is subcultured since the protracted course of the disease permits sensitivity tests against various antibiotics

4 In most instances the invading microbe is the Streptococcus viridans which responds to high and sustained concentrations of peni cillin However a minority of bacteremias reveal resistant strains of streptococci (such as S fecalis and the subacute bacterial endocarditis subgroup identified by Loewe) or other bacteria such as staphylococci H influenzae gonococci meningococci etc

5 Following isolation identification and tests for sensitivity against available antibiotics scientific anti infective therapy (p 4219) is begun

Practical Management

Prophylaxis

1 Before any surgical procedure including such relatively minor operations as tooth extraction or tonsillectomy patients with a history of rheumatic fever evidences of valvulitis (p 970) or signs of con genital heart disease are given prophylactic anti infective therapy with massive doses of penicillin At least 600 000 units of procaine penicillin G in oil with 2% aluminum monostearate (p 4453) are deposited preoperatively and daily for the first two or three post opera

2 Criteria for the establishment of the diagnosis of atypical verrucous endocarditis include

(a) Continued fever
(b) Cardiac murmurs *suggesting endocarditis*
(c) Repeatedly sterile blood cultures on aerobic anaerobic and forti fied mediums
(d) Rheumatic fever like arthralgias
(e) Fleeting white petechias
(f) Evidences of renal involvement (albuminuria hematuria and *nitrogen retention)*
(g) Signs of dry pericarditis
(h) Cutaneous eruption of acute disseminated lupus erythematosus (Fig 223 p 1019)
(i) Evidences of dermatomyositis (Fig 988 p 3373)
(j) Manifestations of solar sensitivity
(k) History of other hypersensitivity reactions

3 Comparison of the lesions of atypical verrucous endocarditis and those of tuberculin type hypersensitivities reveals a striking parallelism (p 4169)

4 Previous suggestions for intensive chemotherapy of atypical verru cous endocarditis (p 1020) were ill advised Injections of sulfonamide and of gold hold small promise but grave threat

Practical Management

Immediate Care

1 Protect the patient *from* sunlight

2 Attempt to discover sensitizing antigen from history and physical examination Particularly inquire concerning antecedent respiratory infection and local or systemic use of sulfonamides salicylates iodides etc

3 Eliminate or avoid all hyperallergens in diet drug cosmetics and *air Keep the room at a comfortable temperature* Use an air con ditioner with a filter to eliminate pollen Use allergen free linen and bedding Apply sterile petrolatum as a local application to skin lesions

4 Search for a focus of infection which may harbor sensitizing strep tococci particularly in the upper respiratory passages Have a con sultant rhinologist lavage the sinuses after radiography

5 *Even if the evidence is not conclusive be prepared* to implement the allergic hypothesis by advocating surgery of possible foci Con sider carefully tonsillectomy antrotomy sphenoidectomy etc

6 Have the consultant dental surgeon radiograph and examine the teeth Be prepared to remove any suspicious teeth

7 Institute antihistamine therapy using increasing oral doses of benadryl or pyribenzamine Start with 200 mg daily and work up to 800 mg unless untoward responses intervene (p 4216)

8 Until preparations are commercially available make application for cortisone to Merck and Co Rahway N J or to Dr Chester S Keefer Chairman National Academy Allocation Committee 2101 Con

7 Durıng convalescence and after at least three sterıle blood cul tures (but whıle the patıent stıll has effectual blood penıcıllın levels) look for focı of ınfectıon especıally ın teeth and upper respıratory tract Get dental and sınus radıographs and consult wıth dentıst and rhınologıst

8 Remove infected focı ıf dıscovered Preferably return to ıntra venous drıp of penıcıllın (wıthout heparın) for twenty four hours pre operatıvely and forty eıght hours postoperatıvely Preferably have consultant operate under local anesthesıa

9 Before termınatıon of penıcıllın therapy estımate extent of cardıac damage Get electrocardıogram and teleoroentgenogram ın addıtıon to a record of clınıcal fındıngs Cautıon the patıent of recurrence Empha sıze that cure of subacute bacterıal endocardıtıs does not relieve preexıstent cardıac damage

10 Frankly dıscuss wıth patıent and famıly the prophylaxıs of back ward faılure (p 945) and especıally alteratıons ın the Way of Lıfe Instıtute symptomatıc therapy for backward faılure (p 948) ıf necessary

Contınuıng Care (Unfavorable Course)

1 If laboratory reports a penıcıllın resıstant organısm or ıf blood cultures remaın posıtıve consıder supplementatıon or substıtutıon of other antıbıotıcs notably aureomycın chloramphenıcol streptomycın or sulfonamıde If there ıs choıce prefer aureomycın and/or chloram phenıcol sınce they are effectıve orally and produce mınımum antı therapeutıc effects (p 4246) However ıf streptomycın or sulfonamıdes appears clearly superıor ın bacterıologıc reports add or substıtute eıther or both

2 If aureomycın or chloramphenıcol ıs chosen gıve a prımıng dose of 100 mg per kılo (7 gm or 28 products for average adult weıghıng 150 pounds) Instruct the patıent to swallow 2 products every few mınutes wıth mılk soup ıce cream or cream chee e Every three hours thereafter nıght and day repeat the dose of 4 products (1 gm)

3 If streptomycın ıs ındıcated gıve a prımıng ıntramuscular ınjec tıon of 1 gm Maıntaın levels wıth 0 5 gm every sıx or eıght hours closely observıng vestıbular and audıtory mechanısms (p 4610)

4 If sulfonamıde ıs suggested gıve a prımıng ıntravenous dose of 2 5 gm each of sodıum sulfamerazıne and sodıum sulfadıazıne Closely observıng blood and urıne maıntaın hıgh levels wıth oral doses of 0 5 gm of each every three or four hours for a total daıly amount of 6 to 8 gm

5 If durıng ıntravenous drıp patıent has an elevatıon of fever wıth or wıthout a chıll suspect embolızatıon exacerbatıon of the funda mental pathologıc dısturbance or reactıon to antıbıotıc ınfusate

(a) Wıth evıdences of embolızatıon persıst wıth antıbıotıc ınfusate and add heparın as descrıbed ın Immedıate Care (3)

(b) If fundamental dı ease appears actıve ıncrease dose of antı bıotıc or supplement wıth another antı ınfectıve agent as descrıbed ın 2 and 3 above

tive days if convalescence is uneventful Daily injections however are continued for at least forty eight hours beyond defervescence if the patient is febrile

2 For prevention of hypersensitivity phenomena due to antibiotic or invading microbe give antihistamine preoperatively and postoperatively (200 mg daily of pyribenzamine or benadryl) as soon as the patient can swallow Continue oral doses at least two weeks after last dose of antibiotic

Immediate Care

1 Pending full laboratory reports the patient is preferably hospitalized *Nonspecific measures* for treatment of the infected patient are inaugurated (p 68–73)

2 Introduce massive doses of penicillin sufficient to kill off resistant strains and to prevent organisms from developing bacterial immunity (p 4133) to antibiotic Set up an intravenous drip and infuse a priming or loading dose of at least 1 000 000 units of crystalline penicillin G in 1500 cc of physiologic saline (or distilled water if there are evidences of backward failure) at a rate of 1 cc per minute (1500 cc in 1440 minutes)

3 *If difficulty is encountered with the drip in the nature* of obstruction due to clot add heparin to infusate for its anticoagulant effect For each 500 cc of penicillin infusate use 10 cc or 100 mg of heparin sodium (Lederle Upjohn) or Liquaemin (Roche)

Caution DO NOT USE Heparin in Pitkin Menstruum intravenously

4 Start antihistamine giving 200 mg daily of pyribenzamine or benadryl orally if possible Otherwise inject 5 cc of 1% benadryl intramuscularly thrice daily

Continuing Care (Favorable Course)

1 Continue infusions of penicillin heparin for at least a week and preferably ten days if possible Change the needle to the other arm or a leg every forty eight hours if introduction is not too difficult Do not remove the functioning infusion until the new one is operating freely

2 Continue antihistamine

3 If heparin is used check coagulation time by simple bedside test once daily (p 4572) Discontinue anticoagulant temporarily if clotting does not occur within thirty minutes

4 Repeat blood culture after four days of treatment and weekly thereafter Caution bacteriologist to use penicillinase in medium

5 As soon as first sterile blood culture is reported (usually forty eight hours after sample is drawn) consider discontinuance of infusion if clinical course also is satisfactory Immediately assure maintenance of antibiotic levels by intramuscular deposits of 600 000 units of procaine penicillin G in oil with 2% aluminum monostearate (p 4453) every six hours for at least one week every eight hours for at least one week and every twelve hours for another month

6 Discontinue heparin when intravenous set is removed but continue antihistamine for at least two weeks beyond cessation of antibiotic therapy

fields and positive serologic tests for malignancy refer patient to neuro surgeon for review of neurologic status lumbar puncture (p 3781) and electro-encephalography

9 Pefer patient for tracer diagno is through use of radioactive i otope I^{131}

10 Consider exploratory craniotomy for removal of tumor if possible

11 If surgical excision cannot be accomplished give x ray therapy

THYROID

Practical Management

1 In our experience malignancy of the thyroid is exceedingly rare We have encountered only one proven instance in more than thirty years of clinical practice

2 We believe that the discrepancy between the frequent diagnosis of thyroid malignancy made by surgical pathologists and the infre quent appearance of fatal thyroid carcinomatosis in the autopsy room is the result of erroneous interpretation of microscopic slides

3 The statement that 10 to 15 per cent of thyroid adenomas become malignant cannot be true or practitioners and pathologists of experi ence would be frequent observers of fatality due to the neoplasm whereas even the seasoned internist and the highly experienced patho logist have difficulty recalling instances of fatality due to malignancy of the thyroid gland

4 The diagnosis of thyroid neoplasm must be considered when there are discrete nodules in the gland and with evidences of hyper thyroidism (p 1197) hypothyroidism (p 1191) or pressure disturbances involving the trachea (p 3512)

5 Under any of the above circumstances obtain blood for sero-diagnosis of cancer (p 4431)

6 Estimate the basal metabolic rate (p 719 and p 3738)

7 Get chest x rays in ordinary postero anterior views and in right and left anterior oblique positions to determine pre sure on the trachea and the presence of sub-sternal or intra thoracic extensions

8 In the presence of a rapidly growing lesion of definitive tracheal pressure of positive serodiagnostic reactions for malignancy and par ticularly of uncontrolled hyperthyroidism refer the patient to a hospital equipped to make measurements of uptake of radioactive iodine I^{131}

9 Using I^{131} test sites of the body other than the thyroid gland for evidences of thyroid deposits

10 If the suspicion of malignancy persists insist on thyroidectomy approaching totality Postoperatively obtain treatment with I^{131} which then may be taken up by extrathyroidal metastatic deposits

PANCREAS

Practical Management

1 Note presence of uncontrolled hyperinsulinism (p 1242)

2 Look for a mass in the epigastrium (p 1814)

3 Obtain blood for sero-diagnostic reactions for malignancy (p 4431)

(c) If there are no evidences of embolization or advancing pathology suspect an untoward manifestation due to intravenous infusion (p 3775) or antibiotic Discontinue the drip Resort to intramuscular or oral doses

6 When drip is discontinued if heparinization appears indicated to supplement antibiotic therapy deposit 300 mg of heparin in Pitkin Menstruum subfascially as elsewhere described (p 4203) Continue anticoagulant effect as indicated making deposits daily or every second day according to results of bedside coagulation test (p 4573)

7 At any time if indicated add 500 cc of citrated blood to the infusion to combat anemia or for tonic effect

8 Obsolete are—human convalescent blood human serum or blood from donors actively immunized against specific invader streptococcus antiserum and streptococcus vaccines

ENDOCRINES NEOPLASMS OF

Neoplasms of the organs of internal secretion may produce manifestations of *hyperfunction* (hyperpituitary gigantism acromegaly and basophilism pancreatic hyperinsulinism adrenocortical virilism) *hypofunction* (pituitary dwarfism pancreatic diabetes adrenocortical Addison s disease) and they may become evident through *pressure disturbances* on contiguous structures (tracheal deviation from compression of the thyroid neoplasm or optic atrophy secondary to pituitary tumor growth)

In the presence of internal secretory disturbances the practitioner must determine (1) whether the dysfunction results from altered activity of tumor or non tumor tissue and (2) if neoplastic whether the lesion is benign or malignant

ANTERIOR PITUITARY GLAND

Practical Management

1 Note manifestations of hypersecretion of *acidophile cells* including gigantism and acromegaly (Fig 238 p 1156 and Fig 239 p 1157)

2 Note manifestations of hypersecretion of *basophile cells* including pituitary basophilism or Cushing s disease (Fig 242 p 1161)

3 Note manifestations of anterior pituitary deficiency including pituitary dwarfism (Fig 247 p 1176) adiposogenital syndrome of Frohlich (Fig 244 p 1168) Dercum s disease (adiposis dolorosa) (Fig 246 p 1175) or Simmonds disease (Fig 245 p 1171)

4 Collect blood for serodiagnosis of malignancy (p 4431)

5 X ray sella turcica (Fig 248 p 1177)

6 Refer patient to ophthalmologist for fundus examination and measurement of visual fields (Fig 240 p 1158 and Fig 241 p 1159)

7 Make routine survey of nervous system (Table 173 p 3584)

8 In the presence of evidences of an expanding lesion with increasing clinical manifestations optic nerve involvement narrow of visual

during the time of exposure to allergen and for at least two weeks following last contact with the offending substance

4 For active treatment prescribe doses of antihistamine up to 800 mg daily and apply for cortisone to the Committee in charge of allocations headed by Dr Chester Keefer 2101 Constitution Avenue Washington 25 D C

EPIDEMIC KERATOCONJUNCTIVITIS

[Shipyard Conjunctivitis Epidemic Infectious Conjunctivitis Keratitis Maculosa Keratitis Nummularis]

General Principles of Diagnosis and Therapy

1 Epidemic keratoconjunctivitis is a serious virus infection of the eye that may result in permanent visual defects (Fig 320 p 1624)

2 Before instituting therapy summon the consulting ophthalmologist

3 The virus causing epidemic keratoconjunctivitis is somewhat sensitive to aureomycin Local use produces approximately 60 per cent of cures

Practical Management

Prophylaxis

1 The high infectivity of epidemic keratoconjunctivitis requires that *the patient be isolated and treated as one suffering from a systemic* infectious disease (p 67) Not only must members of the household and immediate contacts be notified of the presence of the infection but also co workers since the virus often is transmitted by mutual handling of tools as in epidemics of shipworkers during World War II

2 Any article handled by the patient must be sterilized or destroyed

Immediate Care

1 Apply aureomycin hydrochloride ointment (3%) to eyelids and surrounding structures

2 Instill into each conjunctival sac 2 to 4 drops of aureomycin borate ophthalmic solution prepared by adding 5 cc of diluent (supplied by the manufacturer) to the vial containing 25 mg of antibiotic Repeat every two hours or oftener if the infection is severe Keep ophthalmic solution in refrigerator and prepare fresh every second day Apply cold compresses to the eyes for ten minutes after instillations

3 Because of the severity and late sequels of the infection supplement local and topical antibiotic therapy with systemic doses of aureomycin or chloramphenicol Give approximately 50 mg per kilogram per day (12 capsules for average adult weighing 150 lbs)

4 In treatment of severe or resistant infections supplement local aureomycin with instillations of 15% sulfacetimide (sulamyd) and anoint lids with 1 2000 bichloride of mercury

4 In the presence of suspicious manifestations consider exploratory laparotomy for possible excision of a pancreatic adenoma or malignancy

PARATHYROID

Practical Management

1 Note symptoms of hyperparathyroidism (p 1225) including hypercalcemia (p 723) osteitis fibrosa cystica (p 1226) with ostealgia and pathologic fractures (p 2846) and nephrocalcinosis (Fig 253 p 1228)
2 Palpate neck for swellings and tumors (p 3514)
3 Obtain blood for sero diagnosis of cancer (p 4431)
4 In the presence of persistent clinical manifestations and positive serologic findings consider exploratory procedure with removal of neoplastic tissue if feasible

ADRENAL MEDULLA AND CORTEX (P 1263)

Practical Management

1 Note symptoms due to hypersecretion of adrenal medullary substance including paroxysmal hypertension (p 1264) or of adrenocortical virilism (p 1268)
2 Note the effect of benodaine on hypertension as a specific test for adrenalmedullary pheochromocytomas (p 4420)
3 Obtain blood for sero diagnostic tests of malignancy
4 Consider reference to the specialist for perirenal insufflation and x ray demonstration of deformitie in the region of the adrenal cortex (p 2245 and p 2254)
5 In the presence of positive and persistent clinical findings with or without positive sero diagnostic reactions for malignancy consider exploration for possible removal of adrenal medullary or adrenocortical neoplasm

EOSINOPHILIC PNEUMONITIS

(Loeffler s Syndrome)

General Principles of Diagnosis and Therapy

1 Regard eosinophilic pneumonitis as a respiratory manifestation of allergic hypersensitivity (p 4167) It may result from exposure to antigen as diverse as pollens bacteria and the wax menstruum used for repository penicillin
2 In the majority of instance the patient afflicted with eosinophilic pneumonitis gives a history or presents findings of other hyper sensitivity phenomena such as vasomotor rhinitis (p 2098) bronchial asthma (p 2101) and sputum eosinophilia
3 Strive to prevent eosinophilic pneumonitis by concurrent administration of antihistamines (200 mg daily of pyribenzamine or benadryl)

2 Immunization with so-called erysipelas vaccine accomplishes no u eful purpo e If an attack with the living organism does not produce significant immunity injections of dead organisms cannot be expected to accomplish this purpose

Immediate Care

1 Inaugurate non specific treatment of the infected individual (p 67)

2 Deposit intramuscularly 600 000 units of procaine penicillin G in aqueous suspension

3 Protect lesion with terile dressing of petroleum jelly

4 Warn members of the household and other contacts of the infectiousness of the lesion Instruct them to avoid contact with patient lesion dre sings and linen

5 Start prophylactic antihistamine therapy giving 200 mg daily of pyribenzamine or benadryl

Continuing Care (Favorable Course)

1 Maintain penicillin levels by making daily deposits of 300 000 to 600 000 units of procaine penicillin G in aqueous suspension

2 Continue antihistamine for at least two weeks following last penicillin deposit

Continuing Care (Unfavorable Cour~e)

1 In the pre ence of ensitivity or resistance to penicillin substitute aureomycin or chloramphenicol rather than sulfonamide The latter is apt to cau e toxic di turbances and delayed allergic hypersensitivity manifestations such as rheumatoid arthritis and periarteritis nodosa Prefer oral doses of aureomycin or chloramphenicol using 50 to 75 mg per kilogram of body weight daily For the average adult weighing 150 lbs priming and daily do es are thus 3 5 to 5 gm (14 to 20 capsules) These may be given in 4 divided doses i e 4 to 5 products every six hours

2 If the patient is gravely ill and cannot swallow inject 100 mg of aureomycin hydrochloride for intravenous use dissolved in 10 cc of 0 75% sodium carbonate the diluent supplied by the manufacturer If this is not available substitute sulfonamide giving a priming intravenous do~e of 2 5 gm each of sulfadiazine and sulfamerazine dissolved in 200 cc of sterile diluent (physiologic saline 5% dextrose or preferably molar lactate)

3 As soon as the patient is able to swallow substitute the combination of sulfadiazine and sulfamerazine orally in maintenance doses of 1 gm each every four to six hours or switch to aureomycin or chloramphenicol using 50 to 75 mg per kilogram of body weight per day as de cribed above

4 Obsolete is heterologous antierysipelas serum This preparation is not as effectual as antibiotics and carries the risk of acute hypersensitivity reactions (p 4187)

EPIDEMIC PLEURODYNIA

[Bornholm s Disea.e Devil s Grippe]

General Principles of Diagnosis and Therapy

1 Infrequently observed in the United States the 1947 epidemic of pleurodynia in Ma sachusetts enabled Finn et al to study 114 patients (Arch Int Med 83 305 1949)

2 Efforts to isolate the virus proved unsuccessful

3 As in other epidemics the height of the disease occurred in July and August suggesting an insect vector possibly a mosquito

4 Clinical complaints were primarily chest pain headache cough anorexia nausea and chilliness

5 Prominent objective findings included fever friction rub limited chest expansion lymphadenopathy and abdominal rigidity

6 Positive laboratory information included leukopenia and relative eosinophilia Chest radiographs and cardiograms were uninformative

7 Complications included pericarditis and orchitis

8 All patients recovered without sequels

9 Treatment was symptomatic Use of aureomycin and/or chloram phenicol merits consideration

ERYSIPELAS

[St Anthony Fire]

General Principles of Diagnosis and Therapy

1 The diagnosis of ery ipelas is made by its characteristic clinical appearance (p 167 Fig 19 p 165)

2 So successful is penicillin therapy that erysipelas has been reduced to a benign disea.e Control of acute phase ordinarily re quires only antibiotic deposits and bland applications to local lesion

3 On rare occasions the etiologic hemolytic streptococcus pro duces systemic disturbances On that account the practitioner anti cipates and strives to forestall in idious and delayed manifestations including scarlet fever post scarlatinal nephritis rheumatic fever and streptococcal bacteremia

4 The erysipelas producing streptococcus may behave as an offend ing bacterial antigen producing later tuberculin type allergic hyper sensitivities (p 4169) To prevent delayed and potentially grave equels as far as is possible routine antihistamine therapy is warranted even in seemingly mild inva ions

Practical Management

Prophylaxis

1 Warn patient and attendants against auto inoculation through handling wound or dressings

7 In the absence of definitive evidences of sensitization to the pro tein of the tubercle bacillus follow steps uggested in management of erythema multiforme exudativum and erythema nodosum

ERYTHEMA MULTIFORME EXUDATIVUM

[Behcet s Disease Ectodermosis Erosiva Pluriorificialis Stevens Johnson Disease Reiter s Syndrome]

General Principles of Diagnosis and Therapy

1 A critical review of the various syndromes listed in the sub title indicates a marked similarity between each and all and suggests that the group is probably a single clinical entity characterized by a variety of lesions that occur in eyes mouth and genitals

2 Among clinical manifestations which each syndrome may reveal at one time or another are vesicobullous eruptions pseudomembrane formations erythema nodosum like lesions pyoderms maculopapular eruptions urticarias cheilitis gingivitis glossitis ulcerations of pharynx lips and tongue canker sores in mouth nonspecific ure thritis herpes like vesicles of genitals balanitis vaginal and penile ulcers balanoposthitis tracheobronchitis pneumonitis bilateral relaps ing conjunctivitis corneal ulcers hypopyon iritis episcleritis ker atitis uveitis iridocyclitis choroiditis symblepharon neuroretinitis arthralgias and rheumatoid arthritis

3 From this tabulation of clinical manifestations it becomes apparent that the organism has a predilection for the tegumentary system and for mucous surfaces of upper digestive and respiratory tracts and for those of the reproductive systems both male and female

4 Characteristic of the various syndromes is the fact that laboratory examinations reveal nothing of importance Attempts to isolate possible pathogenic organisms have proven futile

5 There i more than a suggestion that each of the e syndromes is a manife tation of allergic hypersensitivity For the present it seems worthwhile to treat the patient suffering from any of these syndromes as one who is afflicted with a perversion of mechanisms of bodily defense most likely against the protein of some living microbic invader

Practical Management

1 Question the patient concerning any previous manifestations of acute histamine type or chronic tuberculin type hypersensitivity (p 4169)

2 Particularly inquire into recent infection of upper respiratory passages

3 Look for foci of infection in nose accessory nasal sinu es pros tate uterine cervix teeth and tonsils

4 *Discovering a focus* consider drainage or extirpation

5 Under any circumstance continue antihistamine for at least ten days after the last dose of antibiotic

6 Reexamine the patient after convalescence to detect any sequels in blood urine or heart

7 In erysipelas involving the lower extremities look for an underlying dermatophytosis If discovered treat with fungicides to prevent recurrence

ERYSIPELOID

General Principles of Diagnosis and Treatment

1 Erysipeloid not to be confused with erysipelas is a relatively common cutaneous infection due to Erysipelothrix rhusiopathiae The causative organism is a gram positive non spore forming bacillus

2 Erysipelothrix is penicillin sensitive in the test tube Clinically satisfactory treatment results are obtained with moderate sized doses of antibiotic

3 Sulfonamides are ineffective Heterologous immune serum (Pitman Moore) is relatively ineffectual as compared with penicillin and carries the hazard of hypersensitivity manifestations (p 4187)

4 Daily intramuscular deposits of 300 000 to 600 000 units of procaine penicillin G in aqueous suspension suffice for specific effects

ERYTHEMA INDURATUM

[Bazin s Disease Tuberculosis Indurativa Subcutanea]

General Principles of Diagnosis and Therapy

1 Regard erythema induratum as a cutaneous manifestation of chronic tuberculin type allergic hypersensitivity (p 4163) (Fig 953 p 3263 and p 3271)

2 Obtain chest films Have sputum examined for tubercle bacilli and perform the cutaneous tuberculin test

3 If laboratory and clinical data suggest sensitization to the protein of tubercle bacillus treat patient as tuberculous (p 4597)

4 Additionally institute a trial with antihistamine prescribing 200 mg daily doses of pyribenzamine or benadryl

5 Consider desensitization with tuberculin (p 4608)

6 Supplement with large doses of calciferol Prescribe oral tablets of 50 000 U S P units (Kremers Urban) thrice daily or make daily intramuscular injections of 0 1 to 0 3 cc of a solution containing 500 000 units per cc (Kremers Urban) During calciferol therapy watch patient carefully for manifestations of hypercalcemia including nausea anorexia headache polyuria diarrhea crystalluria and nephrocalcinosis

ESTROGENS

1 Although a number of synthetic estrogens have been Council approved since the previous listing (Table 140 p 2515) none po sesses significant advantages over tho e described New products include *benzestrol* (Lederle) tablets of 2 and 5 mg *dinestrol* tablets of 0 1 and 0 5 mg (Rare Chemicals Carroll Smith White) *ethinyl estradiol* or *e tinyl* (Schering) tablets of 0 02 and 0 05 mg *hexestrol* (Merrell and Massengill) tablets of 0 2 and 3 mg *monomestrol* or *mestilbol* (Wallace & Tiernan) in tablets of 0 25 to 5 mg *promethestrol dipropionate* or *meprane* (Reed & Carnrick) in tablets of 1 mg

2 Synthetic preparations have the advantage of being more accurate and less expensive

3 Unless there is reason for observing the patient personally estrogen therapy by mouth is advi ed It is as effective as that given parenterally

4 We find ourselves in complete agreement with the Council report that claims for therapeutic results (of estrogen therapy) have been often exaggerated and confusing Definite and consistently reliable results have been obtained in only a relatively small number of conditions

5 We rarely employ estrogens in the treatment of the female menopause (p 2525) Most symptoms respond to psychotherapy or administration of a simple sedative such as phenobarbital In the rare instance where symptoms are persistent or incapacitating our preference is for injection or oral administration of androgen (p 4192) Male sex hormone is anticarcinogenic for the female as opposed to the potentially carcinogenic activity of estrogen in the female Doses as small as 5 mg taken 3 times weekly usually suffice for symptomatic control without any hazard of masculinization (p 4194) If estrogen is used prescribe daily oral doses of 0 5 mg diethylstilbestrol or 0 02 mg estinyl for a limited period Prolonged administration and/or rapid withdrawal may be responsible for significant uterine bleeding (p 2565 and 2567)

6 For treatment of atrophic vaginiti (p 2600) daily oral doses of 0 5 mg of diethylstilbe trol for several weeks suffice for symptomatic relief Smaller quantities may be employed intravaginally if desired (0 2 mg of estrone at night)

7 In secondary amenorrhea (p 2618) in which estrogen is unfortunately useful in only a few amenorrheal women try intramu cular injections of 2 5 mg of estradiol benzoate and 12 5 mg of progesterone on two successive days If parenteral medication is impractical prescribe orally 2 mg of diethylstilbestrol daily for fifteen days followed by 60 mg of pregneninolone daily for five days

8 For postpartum inhibition of lactation prefer androgen (p 4194) If estrogen is substituted prescribe orally 1 mg of diethylstilbestrol 3 times daily for a week Thereafter reduce daily dose to 1 mg for several day until lactation has been completely suppressed

9 Kimbrough and Israel (J A M A 138 1216 1948) list several pre

5 Under any circumstance prescribe antihistamine orally using daily doses of 200 mg of pyribenzamine or benadryl (p 4213)

6 In the presence of active evidences of infection consider antibiotic therapy using feebly allergenic anti infective agents particularly aureomycin or chloramphenicol Avoid if possible hyperallergenic sulfonamides

7 In dealing with infections involving the eye use aureomycin borate in ophthalmic solution topically For systemic supplementation give aureomycin or chloramphenicol orally approximating doses of 25 to 50 mg per kilogram of body weight (2 to 4 capsules four times daily)

8 With failure of antibiotic therapy using aureomycin and chloramphenicol resort to penicillin mindful of the fact that the latter is capable of producing acute histamine type hypersensitivities and that penicillin in large doses has been without appreciable effect

9 Against these unfavorable opinions relative to sulfonamide and penicillin note the statement of Wright (Arch Int Med 79 510 1947) who observed recovery following use of sulfonamides and penicillin administered systemically and topically in eight of nine patients

ERYTHEMA NODOSUM

General Principles of Diagnosis and Therapy

1 Erythema nodosum (Fig 989 p 3375) is probably a cutaneous manifestation of tuberculin type allergic hypersensitivity (p 4169)

2 The tubercle bacillus may be one of the provocative allergens but more often the offending substance is the protein of the hemolytic streptococcus or a drug antigen such as bromide iodide sulfonamide salicylate diphtheria antitoxin Frei antigen and other vaccines and serums (p 3380)

3 In a recent study of 155 patients 86 per cent were women About half of the afflicted had had a previous upper respiratory infection and 25 per cent harbored hemolytic streptococci in their throats Tuberculosis was an uncommon antecedent and rheumatic heart disease a rare sequel

4 We are inclined to agree with Reimann who states that erythema nodosum is probably a manifestation of hypersensitivity caused by a variety of infections and chemical agents conditioned by local trauma and personal predisposition

5 Prophylaxis is best accomplished by avoidance of provocative antigens particularly of the drugs above mentioned and by administration of antihistamine during the course of hemolytic streptococcal infection and for a period of at least two weeks thereafter

6 For active treatment additional administration of antihistamine is recommended with daily doses up to 800 mg of pyribenzamine or benadryl Locally lesions are protected by bland dressings and ointments avoiding further sensitization through use of potential allergens such as sulfonamide ointments iodine and the like

7 At the time of radical mastectomy consider surgical castration in women of child bearing age Otherwise advise irradiation of ovaries post-operatively Immediately start androgen therapy by mouth or preferably by injection

NEOPLASMS OF THE INTERNAL AND EXTERNAL FEMALE GENITALS

1 As part of the routine physical examination observe uterine cervix by vaginoscopy Try to avoid lubricants while introducing speculum

2 Note any vulvovaginal lesions (Figs 627 and 628 p 2552 Fig 631 p 2560)

3 Get blood for serodiagnosis of syphilis and malignancy (p 4431)

4 Always suspect venereal lesions Get darkfield examination for spirochetes (Fig 7 p 46) direct preads for Donovan bodies of granuloma inguinale (Fig 9 H p 48 and Fig 73 p 475) and Frei test (Fig 72 D p 470)

5 If findings are completely normal take a specimen for exfoliative cytodiagnosis by the method of Ayer (p 4430)

6 If there is visible ulceration or a demonstrable neoplasm obtain a specimen by method of Papanicolaou or by sponge biopsy technic (p 4430)

7 If there are positive findings by any method of cytodiagno is insist on a surgical biopsy before proceeding further

8 With positive finding by any method arrange for a round table consultation with consulting surgeon and roentgen therapist Consider irradiation therapy alone by x ray or radium radical surgical excision with or without irradiation and with or without castration

9 Following vaginoscopy make a bimanual examination of internal genitals Question the patient concerning any change in menstrual cycle particularly stressing menorrhagia (p 2557) metrorrhagia (p 2557) *and recently developing dysmenorrhea* (p 2561)

10 In the presence of any positive findings consider diagnostic dilatation and curettage with microscopic examination of scrapings

11 In the presence of tumors or swellings involving uterus ovaries or fallopian tubes (p 2621) consider exploratory laparotomy

FILARIASIS

[Elephantiasis Elephantoid Fever]

General Principles of Diagnosis and Therapy

1 Invasion of human subcutaneous tissues by helminths (Fig 974 p 3320) produces filariasis (Fig 977 p 3323 Figs 975 and 976 p 3322) loaiasis (Fig 978 p 3324 and Fig 979 p 3325) calabar swelling (p 3325) onchocerciasis or blinding filaria (Fig 980 p 3326) and dracontiasis (Fig 981 p 3327)

valent abuses in clinical applications of estrogen These include failure to limit duration of treatment rapid withdrawal after initiation use in premenopausal menstrual irregularity administration to patients with residual endometriosis carcinomatous histories palpable benign tumors of breasts or internal genitals and those with hepatic insufficiency These authors conclude their remarkably fine article with the statement that the regrettable use of estrogen as an all purpose female tonic is to be condemned

10 In the male estrogen may be used for treatment of the rare patient who suffers significantly from the male climacteric (p 2414) Additionally estrogen therapy is of proven value in controlling the growth of generalized metastases from prostatic malignancy However even in the male estrogen therapy may be carcinogenic since patients have been reported with secondary malignancy of the breast unrelated to the primary prostatic cancer

FEMALE REPRODUCTIVE SYSTEM NEOPLASMS OF

Accessibility of the structures of the female reproductive system affords the practitioner his best opportunity for early diagnosis of *asymptomatic malignancy The seasoned practitioner never* omits palpation of the female breast visual observation of uterine cervix and bimanual palpation of uterus adnexa and pelvic peritoneum In addition spreads are made bi annually of the uterine cervix for examination by Ayer or Papanicolaou technics

NEOPLASMS OF FEMALE BREAST

Practical Management

1 During each routine examination palpate the female breasts Perform palpatory transillumination in the darkroom compressing mammary tissue over the source of light noting any opaque areas

2 If any palpable abnormalities are detected refer the patient immediately to the specialist Do not await the criteria of late malignancy (retraction of nipples bloody discharge and axillary lymphadenopathy) These last are actually late manifestations and in their presence the chance for radical cure already has been significantly sacrificed

3 Obtain blood for serodiagnosis of malignancy (p 1431)

4 Get chest x ray for evidences of tuberculous infection and for comparison later on suspicion of pulmonary metastases

5 In the presence of positive findings insist on exploratory procedure in order to obtain satisfactory tissue for microscopic diagnosis Do not compromise on needle biopsy

6 At the time of exploration be prepared for radical surgery if microscopic examination is suspicious or definitively positive

5 In convalescence suggest prophylactic use of insecticides to ward off mosquito fly and gnat vectors Warn patients with dracontiasis to avoid bathing in waters harboring infected crustaceans

FOOD ALLERGY

Food allergies are particularly common in pediatric practice where many children are found to be sensitive to proteins of milk and eggs Therapeutic objectives in the management of these allergic hypersensitivities include elimination of non-essential sensitizing agents substitution of a less sensitizing essential foodstuff for offending allergen desensitization or hyposensitization in the case of an essential food and prophylaxis and palliation with adrenergens and antihistamines

Principles of Diagnosis and Treatment

1 Identify offending allergen by history or elimination diets (p 562 and 683)

2 Verify inferential data with scratch tests if necessary (p 557)

3 Eliminate sensitizing ingestant (p 563)

4 If suspected food is essential as in the case of milk substitute goat s milk or preferably a milk free food made from soy beans (p 2754) or other proteins such as sobee mull oy and nutramigen

5 If manifestations of hypersensitivity persist after elimination or substitution prescribe antihistamine with or without adrenergen and/or procaine as in serum sickness (p 4519)

6 In the case of dissatisfaction with substitutes for an essential food stuff such as cow s milk try alimentary desensitization by ingestion of highly diluted antigen Begin with *1 drop in 1 quart (1000 cc)* of water Increase by drop doses daily to tolerance Concurrently prescribe daily oral doses of histamine antagonists

FOOT AND MOUTH DISEASE

[Epizootic Eczema Epizootic Aphthae Aphthous Fever Epizootic Stomatitis]

General Principles of Diagnosis and Therapy

1 Foot and mouth disease is caused by a dermotropic virus (p 437 and Fig 345 p 1672)

2 The affliction is of little clinical importance but of considerable veterinary significance when it involves cloven footed animals especially cattle pigs sheep and goats

3 Boiling or pasteurization of farm products controls the disease in the human population

2 The diagnosis of filariasis is made by finding microfilaria in circulating blood (p 3324) and by demonstration of skin sensitivity

3 Until recently treatment was both unsatisfactory and hazardous through necessary use of antimonials With introduction of hetrazan there is promise of greater efficacy with almost negligible toxicity

Practical Management

Immediate Care

1 Hetrazan (diethylcarbamazine) a commercially available preparation of 1 diethylcarbamyl 4 methyl piperazine hydrochloride is marketed in tablets of 50 mg (Lederle) For the average individual weighing 150 lbs three or four 50 mg tablets taken three times daily for twenty one days appears an optimum schedule

2 With this dosage microfilarial counts are reduced and after one week of treatment most blood specimens are completely clear

3 Systemic reactions to hetrazan are mild They include headache nausea and malaise

4 In some instances there may be aggravation of existing swelling fever and pain with simulation of an attack of filariasis A possible explanation for this recrudescence is hypersensitivity from release of filarial protein

5 Because of hypersensitivity reactions which may accompany hetrazan therapy simultaneously order antihistamine (200 mg daily of pyribenzamine or benadryl)

Continuing Care (Unfavorable Course)

1 Repeat hetrazan course after a few weeks if microfilaria reappear in the blood or symptoms recur Hetrazan also may be employed prophylactically at the beginning and end of mosquito seasons since the latter are the vectors which transmit the pathogen

2 Patients resistant to hetrazan must be given an antimonial preferably ethylstibamine (neostibosan Bayer 693) Prepare a 5% solution by dissolving 0 2 gm in 4 cc of sterile distilled water Inject this intravenously If there are no toxic symptoms increase the dose to 0 3 gm in 6 cc of distilled water and repeat daily for ten to seventeen days

3 *If intravenous ethylstibamine injections are inconvenient or accompanied* by reactions prepare a 25% solution by dissolving the contents of 1 ampul (containing 0 3 gm) in 1 2 cc of sterile distilled water Inject this intramuscularly in the same dose used for intravenous administration

4 If there is treatment failure with hetrazan and pentavalent antimonial try a trivalent preparation such as anthiolamine (lithium antimony thiomalate) Inject intramuscularly 1 5 cc of 6% solution as a probatory dose If there are no toxic manifestations increase to 3 cc and give daily intramuscular injections for one month Should toxic manifestations of antimony poisoning arise use BAL as the antidote (p 4251)

technical facilities are completely inadequate the use of STB a tri valent derivative of acetarsone with the chemical formula 4-oxy 3 acetylaminophenylarsenoxide is advi ed

7 STB is given in a single daily dose of 10 to 20 mg per kilogram of body weight (0 7 to 1 4 gm for the average adult weighing 150 lbs) Doses are repeated daily for five days This amount produced cicatri zation in infectiou yaws and effective healing of fourteen of fifteen patients with crab yaws

FUMIGACIN

Fumigacin an antibiotic derived from Aspergillus fumigatus is under experimental investigation for the treatment of tuberculosis It is not commercially available

FUNGICIDES

The ideal fungicide for treatment of dermatophytoses should possess the following properties Effective destruction of the pathogens nonirritability and nonantigenicity acidity and nonabsorbability

FUNGICIDES FOR TOPICAL USE

Fungicide	Comment
Aluminum Acetate U S P	See Burow s olution
Ammoniated Mercury U S P	Use as U S P 3 to 10% ointment when there is superimposed secondary infection, prefer less toxic bacitracin
Aureomycin Ointment N N R (3%)	Sensitization to aureomycin may preclude its u e sy temically when the need is greater Prefer bacitracin for topical use
Bacitracin N N R.	Prefer for secondary bacterial infection reserve penicillin streptomycin and aureomycin for sys temic use
Benzoic Acid U S P	See Whitfield s ointment
Boric Acid U S P	As 3 wet dressing or 10% ointment relatively ineffectual no advantage over saline solution and petroleum jelly re pectively
Burow s Solution N F	5% aluminum subacetate relatively ineffectual and *somewhat irritating no advantage over saline solu tion* as a wet dressing
Caprylic Acid	Effective non toxic non irritating and non sensi tizing fungicide One of the pref rred products Prescribe as the commercial preparations sopronol or naprylate
Carfusin N N R (Carbol fuchsin Paint)	Council-accepted fungicide containing 1% boric acid, 4 5% phenol 10% resorcinol 0 3% fuchsin 5% acetone and water Needlessly complicated though tinctorially attractive If used, apply to isolated lesions and opposing skin surfaces (inter digitally intercrurally etc)

4 Ruthless slaughter of susceptible host is the most succesful means of controlling epizootics (Waldmann)

5 Because the disease is benign in the human symptomatic therapy suffices (p 438) Severe invasions particularly in the debilitated merit therapeutic trial of aureomycin or chloramphenicol in doses approximating 25 to 50 mg per kilogram of body weight (2 to 4 products 4 times daily)

FRAMBESIA

[Yaws]

General Principles of Diagnosis and Therapy

1 As in the case of other treponematoses notably syphilis frambesia yields spectacularly to penicillin therapy

2 Both systemic manifestations and the characteristic dermatosis (Fig 50 p 352) respond rapidly though serology may remain positive for some time af er lesions have healed

3 The conduct of penicillin therapy depends a great deal upon available facilities cost of therapy and patient cooperation Since the majority of those who suffer from yaws are ambulatory the simplest schedules provide most satisfactory over all results

Practical Management

1 If aqueous crystalline penicillin G is employed give intramuscular deposits of 100 000 units twice daily for ten days to total 2 400 000 units

2 Where the patient can only be seen once daily substitute crystalline procaine penicillin G in aqueous suspension and make daily deposits of 300 000 units for ten days

3 In outlying communities where patients have even greater difficulty in obtaining medical care use crystalline procaine penicillin G in oil with 2% aluminum monostearate While there are no current reports of treatment with this modality it is quite likely that two weekly injections for two or preferably three weeks will accomplish as much as the daily or twice daily injections of aqueous solutions or suspensions

4 Where there are no facilities for injection missionaries and lay public health officers may experiment with oral penicillin in probatory doses of 250 000 to 500 000 units once or twice daily for a ten day period

5 Reserve arsenotherapy for the rare penicillin resistant infection Give intravenously 60 mg of a preparation of arsenoxide either mapharsen or clorarsen Introduce arsenical three times weekly to total 180 mg for primary and secondary yaws Older infections require eight weekly intravenous injections with supplementary intramuscular depo its of bi muth for an additional eight weeks

6 For mass therapy where cost is an important consideration and

FUNGICIDES FOR TOPICAL USE (*Continued*)

Fungicide	Comment
Phenol U S P	Too toxic for local use
Salicylanilide	Particularly effective against M audonin and most useful in infections of hairy surfaces See Salundek.
Salundek ointment (Wallace & Tiernan)	Contains 5% undecylenic acid 25% zinc undecylenate and 5% salicylanilide in a carbowax base with wetting agent Especially useful in T capitis
Sopronol (Wyeth)	Commercial product containing propionate and caprylate available as ointment, solution and powder effective fungicide non toxic non irritating and non sensitizing
Streptomycin Ointment N N R	Sensitization may preclude later use as systemic anti infective agent prefer bacitracin or tyrothricin
Tar	Little fungicidal activity use only as keratolytic in chronic dermatitis
T C A P Ointment (Wallace)	Commercial ointment containing 2 2% trimethyl cetyl ammonium pentachlorphenate and 1% undecylenic acid effective non irritating non antigenic and effectual fungicide
Thymol	Mild fungicide not comparable with desenex or sopronol
Timofax (Burroughs Wellcome)	10% undecylenic acid powder and ointment effective non toxic non irritating and non sensitizing fungicide
Tyrothricin	Use as 2% solution or 0 5% cream as effective bactericide
Undecylenic Acid	See Desenex
Whitfield s Ointment	6% salicylic acid and 12% benzoic acid mildly fungicidal but quite keratolytic and irritant may produce maceration and treatment dermatitis prefer sopronol desenex, timofax and TCAP
Zinc Undecate N N R	See Desenex
X ray	For epilation in chronic persistent dermatophytoses Rarely needed if there is intelligent fungicidal therapy and adequate patient cooperation

FUNGUS INFECTIONS

Superficial fungus infections (dermatophytoses) are seen as every day experiences in private practice Experts with special laboratory facilities frequently recognize systemic mycoses in patients presenting puzzling respiratory skeletal and articular syndromes

DERMATOPHYTOSIS CUTANEOUS

The superficial dermatophytoses (p 3293) include *ringworm of the body* (tinea corporis tinea circinata Fig 962 p 3294) *groin* (tinea cruris eczema cruris Dhobie itch Fig 963 p 3295) *feet* (tinea pedis dermatophytosis pedis athlete s foot Fig 962 B p 3294) *scalp* (tinea capitis Fig 962 F p 3294) *beard* (tinea barbi tinea sycosis barber s itch Fig 964 p 3303) *nails* (onychomycosis Fig 962 H

FUNGICIDES FOR TOPICAL USE (*Continued*)

Fungicide	Comment
Castellani Paint	See Carfusin
Ceepryn	Effective bactericide available as 1 1000 jelly or wet dressing not as effective as fungicides of choice
Chrysarobin U S P	Not particularly effective stains skin, capable of postabsorptive toxic effect after prolonged use not recommended
Circulin	New antibiotic not commercially available may have future possibilities as fungicide
Cresatin N N R	Potentially toxic cresol derivative (Meta cresylacetate) for application to limited areas as external auditory canal
Dalyde (Dibromsalicyl aldehyde) (Hynson)	Available as 2% ointment or powder for bactericidal activity in secondary infection some fungicidal efficacy but not comparable to preparations of choice
Danish Ointment	Essentially a sulfide has postabsorptive toxic potential after prolonged use not comparable to preparations of choice
Desenex N N R (Wallace and Tiernan)	Highly recommended commercial preparation of undecylenic acid available as 20% ointment and powder non allergenic non irritant and non productive of post absorptive toxic effects after prolonged use one of the preparations of choice
Gentian Violet U S P (Methylrosanilin)	For local use in 1% solution in 20% alcohol fractionally attractive but distinctly not a preparation of choice use as carfusin
Ichthyol N F	Offensive preparation not particularly efficacious not recommended.
Iodine U S P	Locally destructive and keratolytic at most employ for occasional application to stubborn lesion not recommended for protracted use over extensive body surfaces
Methylrosanilin U S P	See Gentian violet
Mercurials	May cause contact dermatitis local irritation and postabsorptive toxic manifestations after prolonged use not recommended
Naprylate (Strasenburgh)	Commercial preparation containing mixture of sodium and zinc caprylates Available in ointment powder and 20% solution A preparation of choice because of fungicidal activity uncomplicated by local irritation antigenic potential or postabsorptive toxic effects after prolonged use
Pragmatar	A non staining tar distillate that does not compare for fungicidal activity with preparations of choice use for symptomatic relief of subacute or chronic dermatitis accompanying fungus infection
Propionic Acid	Essential ingredient of sopronol effective and favored fungicide
Resorcin N.F	Not particularly effective as a fungicide capable of postabsorptive toxic effect after prolonged use not recommended
Penicillin Ointment U S P	Capable of sensitization precluding later use in more serious infections prefer bacitracin
Petrolatum U S P	Sterile best bland ointment for protective use in subacute and chronic dermatitis accompanying fungus infections

Acidity since fungi thrive in an alkaline medium

Nonabsorbability since treatment must be prolonged and repeated without hazard to host tissues

Of the listed preparations these exacting qualifications are best met by caprylic undecylenic and propionic acids available in the com mercial preparations sopronol desenex timofax naprylate and TCAP and in more recently introduced products containing salicylanilide e pecially useful in the management of infections of the hirsute skin

Relatively feeble are many popular preparations such as boric acid Burow s solution ichthyol tar and thymol excessively irritating are mercurials iodides phenols (cresatin) dyes (gentian violet chrysa robin) sulfides (Danish ointment) resorcin and salicylic and benzoic acids (Whitfield s ointment) With the preferred fungicides bacitracin or tyrothricin is useful as the topical bactericide reserving penicillin aureomycin and streptomycin for systemic use when the need is greater

Practical Management

1 Cleanse skin thoroughly with soapless detergent (acidolate aquaphor dermolate lowila phisoderm) Avoid alkaline soaps

2 If there are evidences of a treatment dermatitis or excessive maceration and scaling postpone use of fungicide until local irritation has subsided under the influence of dressings of sterile saline solution milk or petrolatum

3 If there is significant bacterial secondary infection particularly with lymphangitis or lymphadenitis concentrate on bactericides using bacitracin or tyrothricin locally as ointment or wet dressing Deposit 300 000 to 600 000 units of procaine penicillin G in aqueous suspension once daily

4 When treatment dermatitis and secondary bacterial infection have abated apply fungicide u ing nonirritating hypo allergenic preparations such as desenex sopronol naprylate timofax or TCAP If lesions are moist use fungicide in ointment form and separate oppos ing skin surfaces with wisps of cotton or lamb s wool If lesions are dry use powder but prevent caking by eparation of surfaces as described above

5 Protect sterile dermatophytids with sterile petrolatum antihista minic or fungicidal ointments Administer antihistamine daily in 200 mg do es of pyribenzamine or benadryl

6 Instruct patient in methods of avoiding re infection boil linen especially socks apply fungicidal powder to shoes (p 3308) treat other members of household or other contacts in industry (dressing rooms lavatories etc)

7 Prevent auto inoculation by thorough hand washing after handl ing infected parts

8 Insist on weight reduction in the obese suffering from crotch inframammary or interdigital fungus infections

9 Treat irritating discharges that tend to favor fungus growth These include leukorrhea and other vaginal discharges moisture in

p 3294) *external auditory canal* (otomycosis myringomycosis p 3305) *axillary hair* (lepothrix trichosis axillaris p 3305) *tinea versicolor* (pityriasis versicolor chromophytosis Fig 962 D p 3294) *erythrasma* (p 3301) *tinea imbricata* (p 3307) *moniliasis* (Fig 962 E p 3294) and *favus* (Fig 962 G p 3294)

General Principles of Diagnosis and Therapy

1 Fungi are universally distributed in nature They may produce cutaneous disturbances on any body surface but most particularly where opposing dermal segments provide moisture and maceration favorable for mycotic growth

2 Growth of fungi is best accomplished in an alkaline medium Hence alkaline soaps particularly with incomplete drying of inaccessible areas such as those between fingers and toes and in the crotch favor dermatomycosis

3 Fungus infections stimulate a feeble immunity mechanism at best Hence they are prone to be recurrent

4 Fungus infections in the hypersensitive often produce sterile dermatophytids These allergic hypersensitivities do not respond to fungicidal therapy they may be intensified by allergenic fungicides and they persist for as long as fungi are present on any body surface

5 Fungus infections are often complicated additionally by bacterial invasions usually pyogenic

6 In view of these circumstances mere application of fungicide no matter how effectual is insufficient to control dermatophytosis The patient complains of persistence of infection re infection or recurrence With these there is a justifiable demand for use of stronger preparations which usually produce treatment dermatitis providing additional moisture and maceration favorable to fungus growth

7 In the fully developed form in which the patient usually abandons self treatment and seeks professional advice there is the formidable combination of dermatophytosis dermatophytid secondary bacterial infection and treatment dermatitis

8 Preliminary to treatment of the initial fungus infection the practitioner must rid his patient of treatment dermatitis and secondary bacterial infections Only then is it possible to attack the dermatophytosis and its secondary dermatophytids

9 There is no dearth of effectual fungicides for topical use on body surfaces and on accessible body cavities Disappointments in practice may be attributed essentially to misunderstanding of therapeutic principles (p 4170) rather than any lack of potency of preparations currently available

The Ideal Fungicide Ideally the fungicide for treatment of dermatophytoses must possess the following properties

Effective destruction of the pathogens

Nonirritability since maceration and scaling invite fungus growth

Nonantigenicity since many patients already have developed hypersensitivity to the fungus in the nature of dermatophytids (Fig 962 C p 3294 Fig 1121 L p 1121)

taken from sinus pus or sputum with or without addition of a few drops of 10% sodium hydroxide (Fig 75 p 486 Fig 76 p 487) Direct examination may be supplemented by gram stains which show gram positive delicate branching filaments Additionally Nocardia asteroides is somewhat acid fast

6 Less reliable than direct examination are culture methods While most yeast like and mold like fungi grow on Sabouraud s glucose agar 1% dextrose agar and standard blood agar at room or incubator tem peratures direct spreads may be positive with negative cultures Rarely is the contrary true

7 In the case of Actinomyces bovis enriched anaerobic media are required Smith recommends veal infusions and brewer s thioglycollate medium

8 The diagnosis may be confirmed by biopsy through identifica tion of the pathogen in sections and by cultures taken from deeper tissues

DIAGNOSTIC PROCEDURES IN SYSTEMIC MYCOSES

Fungus Disease	Direct Spread (A)	Culture (B)	Biopsy	Skin Sensitivity (1 1000) (C D)	Complement Fixation (E)
Actinomycosis	+	Enriched	+	+	0
Aspergillosis	+	+	+	0	0
Blastomycosis	+	+	+	+	+
Candida (Moniliasis)	+	+	+	+	0
Chromoblastomycosis	+	+	+	+	0
Coccidioidomycosis	+	+	+	+	+
Cryptococcosis (Torulosis)	+	+	+	+	0
Geotrichosis	+	+	+	+	0
Histoplasmosis	+	+	+	+	+
Maduromycosis	+	+	+	+	0
Mucormycosis	+	+	+	+	0
Nocardiosis	+	+	+	+	0
Penicilliosis	+	+	+	+	0
Rhinosporidiosis	+	0	0	0	0
Sporotrichosis	+	+	0	+	0

Notes

A The finding of candida geotrichum aspergillus penicillium and mucor does not establish a diagnosis in the direct spread since these fungi may be accidental findings or secondary invaders All others may be regarded as of primary etiologic significance

B Cultures must be kept and examined for at least thirty days before being discarded

C Skin tests have the same limited significance in the diagnosis of systemic mycoses as in the diagnosis of tuberculosis They indicate merely that the patient has become sensitized to the fungus not necessarily that the individual is suffering actively from a fungus invasion

D Cross reactions occur with coccidioides histoplasma and blastomyces With doses of 1 1000 however much of the non specific substance giving cross reactions is eliminated

E Complement fixations in the systemic mycoses are subject to the same inter pretations as complement fixing bodies in syphilis They merely indicate that the patient has developed immune bodies to the antigen of the microbe not neces sarily that presenting symptoms are related to the invader Cross complement fixations occur in patients with a high titer of antibody to histoplasmin

the anal region from hemorrhoids or hemorrhoidal tabs aural discharges in otomycosis etc

10 Prevent hyperhidrosis particularly of hands feet and axillary regions using local applications of 25% aluminum acetate

11 Prevent maceration of hands particularly in dish washing where use of gloves is recommended

12 For fungus infections of hirsute skin prescribe a preparation containing salicylanilide (salundek contains 5% undecylenic acid 25% zinc undecylenate and 5% salicylanilide in a carbowax base with a wetting agent) Clip hair in infected area as short as possible shampoo scalp each night with any soapless detergent above mentioned then rub a liberal amount of fungicide into infected area and over a wide margin of surrounding scalp repeat application next morning Continue treatment for at least two months during which time the patient wears a tight fitting cap at all times Frequently during course of therapy remove loosened infected hairs manually

SYSTEMIC MYCOSES

General Principles of Diagnosis and Therapy

1 A 15 year study of deep fungus infections by Smith of Duke University in Durham North Carolina emphasizes the relative frequency of systemic mycoses Based on 250 000 consecutive admissions to the University Hospital deep fungus infections occurred in the ratio of 1 10 relative to pulmonary tuberculosis 1 2 relative to bronchiectasis and 2 3 relative to pulmonary abscess They were seen much more commonly than certain diseases which command considerably more attention in medical teaching and writing such as polycythemia hemophilia Addison s disease acromegaly and hemochromatosis

2 With overwhelming frequency invasions are caused by actinomyces blastomyces and monilia Of these leading three actinomyces and monilia are endogenous and appear countrywide in like proportions The frequency of exogenously derived blastomyces (from soil or dirt) in the Carolina area is due to the fact that southeastern states are endemic areas for this particular fungus

3 In both endogenous and exogenous fungus infections males predominate The disproportion is no greater than with other systemic diseases in endogenous systemic mycoses but reaches a remarkable disproportion in exogenous types e g 9 1 for blastomyces and maduromycosis 34 1 for chromoblastomycosis and 7 1 for histoplasmosis

4 Countrywide systemic mycoses of endogenous origin are relatively uniformly represented in statistical studies Of exogenous types however *coccidioidomycosis* is seen most frequently in California Arizona New Mexico southwestern Utah and southwestern Texas *histoplasmosis* in the lower two thirds of the Mississippi valley the Ohio river valley and the region of the Appalachians *blastomycosis* in the Mississippi valley in the southeast *chromoblastomycosis maduromycosis* and *rhinosporidiosis* in the south

5 The diagnosis is established best by direct examination of spreads

500 000 units of crystalline penicillin G in tablet form twice or thrice daily or make daily intramuscular deposits of 300 000 to 600 000 units of procaine penicillin G in aqueous suspension if patient can be seen that frequently or for the patient who finds difficulty coming daily for treatment introduce intramuscularly 600 000 units of procaine penicillin G in oil with 2% aluminum monostearate every second or third day for three or four injections

2 Concurrently with penicillin and for at least two weeks thereafter prescribe antihistamine using daily doses of 200 mg of pyribenzamine or benadryl

Continuing Care (Favorable Course)

1 During convalescence survey infected areas for foci which may conceivably harbor Vincent organisms Pay particular attention to teeth and gums Refer the patient to dentist for general hygiene treatment or removal of carious teeth and correction of areas of redundant gum particularly in the region of rear molars Consider tonsillectomy in those with buried or enlarged tonsils with deep crypts containing inspissated matter

Continuing Care (Unfavorable Course)

1 In the rare instance of penicillin sensitivity or resistance substitute aureomycin in doses approximating 25 to 50 mg per kilogram of body weight (8 to 16 products each of 250 mg for average adult weighing 150 lbs)

2 As third choice resort to supplementary arsenotherapy Give intravenous injections daily or every second day for a total of four or five injections of 60 mg of mapharsen or clorarsen Remember that the arsenoxides may cause toxic responses (p 122) Should these appear inject BAL as effective antidote (p 4251)

3 To avoid confusion in interpretation of untoward manifestations confine local therapy to washes of hydrogen or zinc peroxides

GAMMA GLOBULIN FRACTION

[See also Blood]

Available Products

Human Serum Immune Gamma Globulin Fraction U S P (Cutter Wyeth Lederle)

Therapeutics

Human serum immune gamma globulin fraction contains concentrated antibody It is used for passive immunization in certain communicable disease notably measles mumps pertussis and virus hepatitis

9 As to therapy Smith reports encouraging but variable specific therapeutic effect from potassium iodide in actinomycosis aspergillosis blastomycosis moniliasis chromoblastomycoses cryptococcosis (torulosis) geotrichosis maduromycosis mucormycosis nocardiasis and penicilliosis He notes as do other observers that hypersensitive patients may be worsened by iodide and require desensitization with vaccines before iodide therapy is resumed In no instance is the specificity of iodide such as to preclude the use of other available measures

10 Smith reports some encouraging responses to sulfonamide and penicillin Actinomycosis responds unevenly to sulfonamide and penicillin South American blastomycosis to sulfonamide cryptococcosis (torulosis) nocardiasis and sporotrichosis to sulfonamide given in large doses for a long period of time

11 Vaccine therapy is available for any organisms that can be cultured if they accomplish nothing more vaccines reduce hypersensitivity reactions in those who respond poorly to iodide therapy

12 For practical management of specific systemic mycoses consult the material for each individual invader i e actinomycoses coccidioidomycosis etc

FUSOSPIROCHETOSIS

[Vincent s Infection]

General Principles of Diagnosis and Therapy

1 In the management of fusospirochetosis the practitioner is faced with the dual problem of ridding his patient of acute manifestations and of instituting measures to prevent recurrence

2 The invasive micro organisms are sensitive to penicillin aureomycin and arsenicals each of which may be used topically or systemically

3 Prevention of recurrence is dependent upon removal or excision of necrotic tissue upon which organisms depend for continued existence Most often suitable areas for microbic growth are found under redundant gums around areas of pyorrhea in carious teeth and in tonsilar crypts Inasmuch as these nests are relatively inaccessible to topical applications during acute phases of the disease prefer systemic administration of antibiotics Since recurrence of fusospirochetosis is the rule rather than the exception resort to extensive dental hygienic measures or surgical extirpation accompanied by prophylactic antibiotic therapy in convalescence

Practical Management

Immediate Care

1 Place main reliance on penicillin For reasons above mentioned and because of greater incidence of sensitization phenomena from local use of antibiotic prefer systemic administration Order oral doses of

Available Products

Garlicin is not yet commercially available

Pharmacology

Garlicin inhibits growth of bacteria of the colon group It is no inactivated by body fluids ultraviolet irradiation or heating to 70° F Sulfonamides appear to increase its activity

Given orally garlicin enters the blood without penetration into red cells It diffuses into the cerebrospinal fluid and is eliminated in bile and urine It is demonstrable in the urine two hours after administration Elimination reaches a maximum during the sixth hour and decreases rapidly by the end of the day

Therapeutics

Over 300 patients with acute and chronic enterocolitis have been treated with garlicin Those infected with Shigellae showed frank improvement or disappearance of intestinal symptoms by the second day and bacteriologic cure in ix days Patients with Salmonella infections (p 4511) were improved on the second or third day and bacteriologically cured in nine days

It is suggested that a large dose be given on the first day with decreasing amounts on subsequent days For example 20 units every two hours the first day 20 units every three hours on the second third and fourth days 20 units every four hours on the fifth sixth and seventh days 20 units morning and evening on the eighth and ninth days and thereafter when necessary

Toxicology

Garlicin is practically nontoxic Given in doses up to 700 times the maximum therapeutic amount it does not produce untoward effects

GAS GANGRENE

[Clostridiosis]

General Principles of Diagnosis and Therapy

1 No preparation is available for long term prevention of gas gangrene similar to the prophylactic usefulness of tetanus toxoid for establishment of active immunity

2 Parenteral use of penicillin has reduced both the mutilation and mortality of gas gangrene Optimum results are obtained when the antibiotic is u ed with antitoxin supplemented when necessary by thoughtful conservative surgery

3 The chart of the various official preparations of gas gangrene antitoxin reveals that maximum protection is afforded by the combination of pentavalent gas gangrene antitoxin together with tetanus antitoxin Bivalent and trivalent combinations afford no protection against

Each 2 cc of the commercial preparation is the equivalent of 40 cc of original plasma For prevention of measles give 0 1 cc per pound of body weight intramuscularly for modification of measles inject 0 02 cc per pound of body weight to prevent or modify virus hepatitis inject 10 cc intramuscularly in the pre icteric phase if possible to prevent mumps complications inject 40 cc intramuscularly for prevention or treatment of pertussis give 2 5 cc intramuscularly

If human serum immune gamma globulin fraction is not available substitute human immune globulin extracted from placenta Of this give doses at least in multiples of four

GANTRISIN (NU 445)

Gantrisin is a newly developed sulfonamide whose chemical formula is 3 4-dimethyl 5 sulfanilamido isoxazole

Available Products

Gantrisin Tablet 0 5 gm (Roche)

Pharmacology

Gantrisin has a high solubility over a wide *p*H range It does not form concretions and is less toxic than other sulfonamides Its bacterial spectrum parallels that of sulfadiazine (p 4548) It is highly effective against hemolytic streptococci and Streptococcus viridans but is relatively ineffective against Streptococcus fecalis

Therapeutics

Gantrisin has been used mostly in the treatment of urinary infections Given in oral doses of 1 to 2 gm every six hours or by intramuscular or intravenous injection in high concentration (4 gm in 10 cc) it prevents streptococcal bacteremia following tooth extractions In urinary sepsis it is highly effective against E coli Proteus Alkaligenes A aeruginosa but ineffective against Streptococcus fecalis and Pseudomonas which are highly resistant

Toxicity

From available evidence gantrisin is comparatively less toxic than related soluble sulfonamides In the experience of Dowling (Am J M Sci 218 136 1949) untoward manifestations occurred in 4 2% of patients given gantrisin as contrasted with 8 1% from sulfadiazine and 10% from sulfamerazine

GARLICIN

Garlicin is an antibiotic extracted from garlic

caine penicillin G in oil with 2% aluminum monostearate once or twice daily according to severity of infection and patient response

2 Since the purpose of antitoxin therapy is to neutralize toxin elaborated by Clostridia before anti infective capacities of penicillin have been established continued serum therapy appears unnecessary once high levels of antibiotic have been established

3 Continue antihistamine throughout the course of anti infective therapy and for a period of at least two weeks after administration of the last dose

4 In the face of worsening conditions re establish intravenous drip and give massive penicillin therapy using as much as 25 000 000 units of crystalline penicillin G each twenty four hours diluted to approximately 2000 cc with 5% dextrose in physiologic saline

GAS GANGRENE ANTITOXINS

	Cl perfringens (welchii)	Cl septicum	Cl. oedematiens (novyi)	Cl bifermentans (sordelli)	Cl histolyticum	Cl tetanus
	unit per cc					
Bivalent gas gangrene (Lilly)	10 000	10 000	—	—	—	—
Trivalent gas gangrene U S P (National Drug Parke Davis Squibb Wyeth)	10 000	10 000	1 500	—	—	—
Pentavalent gas gangrene U S P (Lederle)	10 000	10 000	1 500	1 500	3 000	—
Tetanus-gas gangrene combined U S P (Cutter Lederle National Drug Lilly Squibb Parke Davis Wyeth)	2 000	2 000	—	—	—	1 500

GASTRIC ANTACIDS

Non absorbable gastric antacids (p 1755) continue to find greatest favor in the treatment of functional gastric hyperacidity and in the management of peptic ulcer (p 1791) Although the market continues to be flooded with widely advertised preparations the Council on Pharmacy and Chemistry has accepted only the following preparations in addition to those previously listed (p 1754) Most of the more recently accepted products have as their base amphoteric aluminum salts as oxides phosphates or amino acetates (glycine)

Cl bifermentans and Cl histolyticum while tetanus gas gangrene combined contains insufficient doses of tetanus antitoxin and bivalent products of gas gangrene

4 Prompt and efficient combined anti infective therapy using penicillin and antitoxin is so highly effective that Anderson and Keefer 1948 state that surgery for the purpose of controlling infection is rarely indicated when penicillin is administered it seems likely that the use of surgery in the treatment of gas gangrene will be limited to removal of avascular tissue into which penicillin cannot penetrate The use of antitoxins to neutralize toxins already in the blood and tissues may serve as an important adjunct to this drug (penicillin) • the effectiveness of penicillin as an antibacterial agent introduce the distinct likelihood that radical surgical procedure such as amputation of an extremity can be largely obviated in the treatment of clostridial infections Antitoxin remains a useful adjunct to penicillin therapy

Practical Management

Immediate Care

1 On suspicion of gas gangrene set up an intravenous drip and give a loading dose of 1 000 000 units of crystalline penicillin G

2 While the penicillin drip is in operation question the patient concerning a history of hypersensitivity reactions or of previous serum injections (p 4187) Meanwhile test with 1 10 horse serum in the conjunctival sac and intracutaneously for objective evidences of hypersensitivity

3 In the presence of manifestations of hypersensitivity desensitize with progressively increasing doses of horse serum given intracutaneously and subcutaneously as elsewhere outlined (p 4191)

4 As soon as it appears safe add gas gangrene antitoxin well diluted to the intravenous drip The preparation of election is pentavalent gas gangrene antitoxin supplemented with tetanus antitoxin if there is suspicion of a mixed infection Only in this way is it possible to deliver effective doses of antibody against all members of the family of Clostridia

5 For prophylaxis of hypersensitivity reactions introduce 5 cc containing 50 mg of benadryl solution into the intravenous drip or deposit intramu cularly Concurrently if the patient is able to swallow prescribe 50 mg of pyribenzamine or benadryl every four hours for at least two weeks after the last dose of anti infective agent has been administered

6 If possible summon the consulting surgeon for a decision concerning treatment of the wound If consultation connot be arranged lay the wound open under anesthesia and arrange for irrigation with half strength hydrogen or zinc peroxide

Continuing Care

1 Maintain penicillin levels by continuation of the intravenous drip or if this is impossible deposit intramuscularly 600 000 units of pro

GENTIAN VIOLET

[Methylrosaniline]

A triphenylmethane rosaniline dye used as anthelmintic in the treat ment of oxyuriasis (pinworm p 1902) strongyloidiasis (p 1905) and clonorchiasis (p 4288)

Available Products

Tablets Gentian Violet (enteric coated) N N R 30 mg (1½ hour Seal in) for strongyloidiasis (4 hr Seal in) for oxyuriasis (National Aniline)

Therapeutics

Two tablets (60 mg) every four hours for eight to seventeen days After one week repeat course if necessary

Toxicology

See p 1895

GEOTRICHOSIS

General Principles of Diagnosis and Therapy

1 Because of the rarity of systemic geotrichosis reports have not yet been made available as to the efficacy of newer anti infective agents Certainly if the practitioner encounters a proven example of this systemic fungous disease (p 505) procedures suggested for actino mycosis (p 4141) or coccidioidomycosis (p 4289) merit consideration

2 For local application paint cutaneous and mucosal lesions with 1% gentian violet

3 In the presence of intestinal lesions prescribe tablets of gentian viol[illegible]rder 2 tablets (60 mg) every four hour for no less than two w

[illegible]es of saturated potassium iodide and intravenous injec [illegible]n iodide have been recommended in geotrichosis as in [illegible] diseases Whether iodide pos esses any curative value

[illegible]erapy of geotricho is is suggested as in *blastomycosis*

GIARDIASIS

[illegible]ntestinal tract with Giardia lamblia (Fig 431 [illegible]manifestations of enterocolitis [illegible] best managed in the manner of amebiasis [illegible]um and/or carbarsone separately or in outlined in detail (p 4183)

GASTRIC ANTACIDS

Preparation	Action and Dosage	Council approved Available Preparations
Aluminum Hydroxide Gel N N R (an aqueous solution containing 3 to 4 4% of aluminum hydroxide with flavoring sweetening and preservative)	Effective antacid does not increase pH sufficient to interfere with peptic digestion does not stimulate rebound compensatory increase in free hydrochloric acid does not produce systemic alkalosis a mild astringent and demulcent favoring mucous coating of inflamed or ulcerated mucosa also tends to produce constipation non toxic though prolonged use of large doses may interfere with absorption of mineral and produce a phosphorus deficiency U e in doses of approximately 1 to 2 teaspoonfuls in a half glass of water or milk every two to four hours may also be given by continuous intragastric drip in dilutions of one part of aluminum hydroxide gel to two or three parts of water at the rate of 15 to 20 drops a minute to total 1500 cc of diluted suspension for twenty four hours	Gel Aluminum Hydroxide (Barlow Maney MacAllister Reserve Research Co Rorer Schieffelin and Upjohn) Creamalin (Winthrop Stearn)
Aluminum Phosphate Gel U S P (contains 3 8 to 4 2% of aluminum phosphate with flavoring sweetening and preservative)	Has antacid astringent and demulcent properties analogous to aluminum hydroxide does not interfere with phosphate absorption acid combining power approximately half that of aluminum hydroxide gel prescribe 4 to 8 teaspoonfuls alone or with water or milk as with gel aluminum hydroxide	Phosphaljel (Wyeth)
Dihydroxyaluminum Amino Acetate N N R	Shares properties of aluminum hydroxide gel may be prescribed in more convenient tablet form ess astringent and hence less constipating buffering action slightly more prompt prescribe 1 to 2 tablets after meals and at bedtime	Alglyn (Brayte) Aspogen (Eaton) Alzinox (Patch) 0 5 gm Tablets
Mucin Aluminum Hydroxide Magnesium Trisilicate N N R (Gastric Mucin 0 16 gm Dried Aluminum Hydroxide Gel 0 25 gm Magnesium Trisilicate 0 45 gm with excipients and flavoring)	Histamine free gastric mucin provides protective coating rapidly reacting aluminum hydroxide and more slowly reacting magnesium trisilicate give a mixture with advantages of both antacids magnesium trisilicate counteracts constipating action of aluminum hydroxide Dose 2 tablets well chewed, every two hours without fluids during the following half hour	Mucotin (Harrower)

GENTIAN VIOLET

[Methylrosaniline]

A triphenylmethane rosaniline dye used as anthelmintic in the treat ment of oxyuriasis (pinworm p 1902) strongyloidiasis (p 1905) and clonorchiasis (p 4288)

Available Products

Tablets Gentian Violet (enteric coated) N N R. 30 mg (1½ hour Seal in) for strongyloidiasis (4 hr Seal in) for oxyuriasis (National Aniline)

Therapeutics

Two tablets (60 mg) every four hours for eight to seventeen days After one week repeat course if necessary

Toxicology

See p 1895

GEOTRICHOSIS

General Principles of Diagnosis and Therapy

1 Because of the rarity of systemic geotrichosis reports have not yet been made available as to the efficacy of newer anti infective agents Certainly if the practitioner encounters a proven example of this systemic fungous disease (p 505) procedures suggested for actino mycosis (p 4141) or coccidioidomycosis (p 4289) merit consideration

2 For local application paint cutaneous and mucosal lesions with 1% gentian violet

3 In the presence of intestinal lesions prescribe tablets of gentian violet Order 2 tablets (60 mg) every four hours for no le s than two weeks

4 Oral doses of saturated potassium iodide and intravenous injec tions of sodium iodide have been recommended in geotrichosis as in other fungous diseases Whether iodide possesses any curative value is dubious

5 Vaccine therapy of geotrichosis is suggested as in blastomycosis (p 4255)

GIARDIASIS

Infestations of the intestinal tract with Giardia lamblia (Fig 431 p 1892) may produce manifestations of enterocolitis

Intestinal giardiasis is best managed in the manner of amebiasis using aureomycin diodoquin and/or carbarsone separately or in combination as elsewhere outlined in detail (p 4183)

GLANDERS

[Farcy]

General Principles of Diagnosis and Therapy

1 Human glanders is rarely encountered except as a laboratory infection However the frightening possibility that a related invasion melioidosis may be introduced as an agency of bacterial warfare adds the element of urgency to attempts to control glanders by anti infective therapy

2 Because of the intense infectivity of M mallei isolate the patient with human glanders and notify health authorities (p 68)

3 Laboratory studies and the few clinical instances of human glanders suggest that infections with M mallei are amenable to treatment with *sulfadiazine* *Because of the potential severity of the disease* introduce intravenously an initial loading dose of 2 5 gm each of sodium sulfamerazine and sodium sulfadiazine in 200 cc of diluent preferably molar lactate Thereafter prescribe orally daily maintenance doses of 3 to 4 gm each of sulfadiazine and sulfamerazine with bicarbonate of soda in 4 equally divided portions

4 Experiences with penicillin provide no encouragement in the treatment of glanders Combined anti infective therapy may be attempted by supplementing sulfonamide with aureomycin or chloramphenicol particularly since the gram negativity of the pathogenic organisms suggest the possibility that these more recently introduced anti infective agents may be more efficacious than penicillin Prescribe doses of no less than 100 mg per kilogram of body weight per day or 4 products every three hours except at 3 A M for the average adult weighing 150 lbs

5 For desperation anti infective therapy consider intramuscular injections of streptomycin Give 1 gm thrice daily during acute phases of the disease The mortality of glanders offers a much greater hazard to the patient than the toxicity of combined antibiotics Successful treatment of one case of glanders with streptomycin combined with penicillin and sulfadiazine has been reported

6 As in other infections give prophylactic doses with antihistamine during antibiotic therapy and for at least two weeks following the last dose Prescribe daily amounts of 200 mg of pyribenzamine benadryl or any other of the antihistamines (p 4212)

GOLD

The history of chrysotherapy is historically fascinating if therapeutically infertile The elixir vitae of alchemists the magic metal of Paracelsus and others at one time or other was reputed to cure syphilis leprosy dipsomania cancer and asthma among other afflictions Such few favorable results as might have been observed were

likely examples of spontaneous healing in concert with potent psy chotherapy!

Presently gold is used therapeutically in the treatment of non disseminated lupus erythematosus and rheumatoid arthritis In either instance indications for its administration are ba ed on the erroneous hypotheses that (1) each syndrome is an atypical form of tuberculosis and (2) gold is specifically bactericidal for the tubercle bacillus

Available Products

Gold Sodium Thiomalate (*Myochrysine*) N N R (Merck) Ampuls of 1 cc volume containing respectively 10 25 50 and 100 mg equivalent to 5 12 5 25 and 50 mg of gold

Gold and Sodium Thiosulfate (*Sanocrysin*) N F (Abbott Merck Searle) Ampuls containing 10 25 50 75 and 100 mg of a 37 4% solution

Lauron (*Endo*) A suspension in esame oil of auriothioglycolanilid containing 54% gold Marketed in treatment sets of four multiple dose vials each containing 5 cc Vial I has 50 mg and the others 150 mg of lauron per cc

Aurothioglucose (*Solganol B Oleosum*) (Schering) Ampuls of 1 5 cc containing 10 25 or 50 mg of a 50% oily suspension for intra muscular injection

Pharmacology

After administration of any available preparation to the human patient 75 to 80% of injected gold is retained indefinitely in kidneys liver and other organs The remainder is excreted chiefly in urine and partially in feces Gold can be demonstrated in blood plasma for periods up to ten months after discontinuance of injection

Gold has no demonstrable pharmacologic action At most an increased bacteriostatic action of blood serum is demonstrable against hemolytic streptococci Even advocates of gold therapy admit that these laboratory findings have no particular application to the therapy of the clinical syndromes for which chrysotherapy has been recom mended Archer s hypothesis (Arch Int Med 84 367 1949) that the production of hepatic damage and/or dysfunction by the therapeutic agent accounts for remissions of arthritis appears confirmed by the clinical observation that patients in whom toxic reactions develop respond best to treatment

Therapeutics

Presently gold therapy has been generally abandoned in tuberculosis but it is retained in the treatment of nondisseminated lupus erythema tosus and rheumatoid arthritis Since it is now known that neither syndrome is an atypical manifestation of tuberculosis observed bene fits cannot be due to alleged bactericidal action on tubercle bacilli According to modern concept each syndrome is the result of chronic tuberculin type allergic hypersensitivity (p 4169) in many instances

to streptococcal antigen Inasmuch as gold is not effectively streptococcidal and to the best of present knowledge has no prophylactic or curative effect on the hypersensitivity reaction it is difficult to account for any therapeutic efficacy except on Archer s concept of induced hepatic damage

Despite absence of demonstrable indications for chrysotherapy particularly in rheumatoid arthritis experienced clinicians such as Cecil state that gold therapy is considered by many to be the most satisfactory single agent in the treatment of rheumatoid arthritis It is particularly valuable in early cases If a patient shows no improvement after two courses of gold therapy further administration of the agent is contraindicated

Against the favorable opinions are several by equally seasoned practitioners such as Bauer who expects the use of gold salts to be abandoned in the not too distant future (J A M A 132 975 1946) of Hench (loc cit) who states his belief that chrysotherapy is justified when rheumatoid arthritis has lasted more than a few months and shows evidences of being progressive provided that the patient understands and is willing to share the risks

Additional evidence of the confusion that exists in the field of chrysotherapy is attested by examination of reported clinical results Thus a favorable outcome is reported by enthusiasts in approximately 35 per cent of instances against 15 per cent by the less optimistic Relapse rates are granted to be high by all but estimates vary between 50 and 80 per cent Toxic reactions are reported as low as 25 to 30 per cent in the experience of some and as 70 to 80 per cent in the experience of others Whichever figures are accepted the practitioner will perhaps be impressed primarily by the incidence of fatal gold reactions admitted to occur in 2 of five hundred cases by Bruce and in 2 of eight hundred cases by Cecil both strong advocates of chrysotherapy

Final judgment of chrysotherapy may be possible when a larger experience has been obtained from use of cortisone in rheumatoid arthritis *It would not be too surprising to find that the more recent* innovation hammers the last nail in the coffin of chrysotherapy

Dosage

Whatever preparation of gold is used the initial dose must no *exceed 5 to 10 mg in order to test the tolerance of the patient* to the preparation Subsequent doses may be increased by increments of 5 to 10 mg to total weekly doses of 25 to 75 mg until 700 to 2000 mg have been administered in a single course After a rest period of six to twelve weeks the course may be repeated A minimum of two courses is generally accepted as essential to the effective management of rheumatoid arthritis The Council presently recommends only intramuscular injections it does not sanction intravenous introduction

Toxicity

The toxicity of gold is very much like that of arsenic (p 122) Among the long and varied list of untoward manifestations are nitritoid crises

toxicoderms including exfoliative dermatitis blood dyscrasias including agranulocytosis thrombocytopenic purpura anemia skin pigmentation (chrysiasis) acute glomerulonephritis and toxic hepatitis

During gold therapy eternal vigilance must be exercised There must be repeated physical surveys urine analyses and blood counts for early detection of toxicity Patients receiving gold therapy are warned of the potential harmful effects of exposure to strong sunlight They must not be given heliotherapy because of the hazards of photo sensitization

There is general agreement that chrysotherapy is contraindicated in the chronic deformed phases of rheumatoid arthritis in nephropathies hepatic insufficiencies blood dyscrasias anemia and acute disseminated lupus erythematosus

Whereas it is generally stated that gold therapy should be undertaken only by the expert it is difficult to understand just how the latter prevents or detects untoward manifestations in any manner that exceeds the capacity of the practitioner It is generally admitted that toxic reactions do not bear a constant relationship to the doses of gold used that there is no known method of preventing toxic reactions and as previously stated fatal gold reactions occur once in 250 to 400 even in the hands of the most experienced

Antidote

Gold therapy has been made considerably safer since introduction of BAL (p 4251) On first appearance of toxic manifestations injections of antidote are indicated in order to prevent treatment deaths In agranulocytosis concurrent injections of penicillin are recommended and transfusions fortified with vitamin K merit consideration in the bleedings of thrombocytopenic purpura

Additionally prophylactic and symptomatic administration of antihistamine is justified under all circumstances Antihistamines cannot possibly interfere with whatever may be the therapeutic principle underlying chrysotherapy and conceivably they may forestall hypersensitivity manifestations

GONOCOCCAL INFECTIONS

Principles of Diagnosis and Therapy

1 Gonococcal infection usually is limited to invasion of the urethra and reproductive tracts In the female it may extend to involve pelvic peritoneum (p 217)

2 On occasions when patient resistance is low and/or organism virulence is increased bacteremia may occur with resulting bacterial endocarditis and/or metastases particularly in the joints

3 The gonococcus is sensitive to penicillin aureomycin/chloramphenicol sulfonamides and streptomycin

4 Penicillin is currently the preparation of choice for treatment of gonorrhea Its cure rate approximates 100 per cent antibiotic fast organisms are rare there is minimum hazard of drug toxicity though minor hypersensitivity reactions may be encountered As contrasted to aureomycin and chloramphenicol penicillin has the advantages of longer observation and greater efficacy in the prevention and cure of concurrent syphilis However unlike aureomycin and chloramphenicol it possesses no treatment potential against the three other venereal infections of chancroid granuloma inguinale and lymphopathia venereum

5 Aureomycin and chloramphenicol alone of available antibiotics attack all five venereal diseases They are preparations of choice in granuloma inguinale lymphopathia venereum and chancroid they possess gonococcicidal capacities though they appear not to be as efficient as penicillin finally they are spirocheticidal but not to the degree that is exhibited by penicillin

6 Except from the standpoint of economy penicillin is the practitioner s first choice in the prevention and treatment of gonococcal infections *Aureomycin and chloramphenicol are alternates* for substitution or supplementation Because of its lesser efficacy its production of fast strains and its greater toxic potential sulfonamide is last choice unless treatment cost is a prime consideration

Practical Management

Prophylaxis

1 For prevention of ophthalmia neonatorum prefer penicillin to conjunctival instillations of silver proteinate (p 1621) Silver salts are le s efficacious and give rise to a higher percentage of treatment conjunctivitis strong solutions introduced through error may produce permanent scarring of cornea with persistent visual defects and even blindness

2 For penicillin prophylaxis of ophthalmia neonatorum inject 100 000 to 250 000 units of crystalline procaine penicillin G in aqueous suspension into the mother during labor or instill several drops of a solution of penicillin containing 2500 units to the cc into both conjunctival sacs immediately after delivery

3 Combine maternal injection and conjunctival instillation if birth passage has been recently contaminated

4 For mass prophylaxis of gonorrheal urethritis use technic employed in the armed forces Prescribe 2 gm of sulfadiazine with a teaspoonful of bicarbonate of soda before the soldier leaves camp Repeat dose on return to camp and at reveille the next morning This routine reduced the incidence of gonorrhea from 171 to 8 per thousand Simultaneously the rate of chancroidal infections fell from 52 to 6 per thousand Sulfonamide however offers no protection against syphilis granuloma inguinale or lymphopathia venereum

5 More impressive than sulfonamide prophylaxis of gonorrhea is that afforded by oral penicillin Ingestion of a single tablet containing

250 000 to 500 000 units of crystalline potassium penicillin G within two hours of exposure reduced the incidence of gonorrhea from 11 9 per one thousand liberties to 2 questionable cases in 2 023 liberties This remarkable prophylactic result was accomplished without toxic manife tations without evidences of sensitization even when penicillin was taken as frequently as three times weekly and without production of penicillin fast bacterial strains Those men who developed gonorrhea despite penicillin prophylaxis responded to active penicillin therapy as effectively as if they had not been previously exposed to antibiotic (Eagle)

6 Whereas simple ingestion of penicillin or sulfonamide tablets is suitable for mass prophylaxis in an army establishment it is not advis able in private practice Sulfonamide offers no protection against syphilis and the relatively small amount of penicillin that is used will not prevent and may mask syphilis Sulfonamide offers some con current prophylaxis against chancroid but penicillin has no effect on the other venereal diseases namely granuloma inguinale lymphopathia venereum and chancroid

7 For individual prophylaxis against all five venereal diseases give 10 daily intramuscular injections each of 600 000 units of cry talline procaine penicillin G in oil with 2% aluminum monostearate Simul taneously prescribe aureomycin or chloramphenicol in doses of 250 to 500 mg 4 times daily for the period of ten days This routine cum bersome and expensive to the patient may serve al o as a deterrent to frequent and promiscuous exposure

8 Insist on weekly examinations for the first four weeks following completion of treatment and monthly examinations thereafter for six months At each visit in addition to physical examination take blood for serologic tests for syphilis

Immediate Care

1 Confirm clinical diagnosis especially of urethritis by demon stration of organism in direct spreads (Fig 8 A p 47) or cultures In our experiences nonspecific urethritis is not too uncommon and an error in diagnosis may cause profound domestic repercussions

2 While a single repository dose of 300 000 units of crystalline procaine penicillin G in aqueous or oily suspension usually suffices to cure gonorrheal vaginitis and urethritis in adults or children this minimum treatment dose is not sufficient for the needs of the private practitioner In addition to the necessity for seeking a cure rate of 100 per cent the individual physician must regard each patient exposed to gonorrhea as a potential victim of syphilis and perhaps of the remain ing venereal diseases He must in consequence vigorously over treat the gonorrheal infection in order to prevent possible development of concurrent venereal infections each of which has a longer period of incubation

3 The course of treatment recommended for individual prophylaxis against all five venereal diseases should be repeated for each person who has acquired a gonorrheal infection More specifically give 10

daily intramuscular injections of 600 000 units of crystalline procaine penicillin G in oil with 2% aluminum monostearate Simultaneously prescribe aureomycin or chloramphenicol in doses of 250 to 500 mg four times daily for the ten day period

4 Concurrently with penicillin therapy and for a period of at least two weeks after the last dose give prophylactic antihistamine as daily doses of 200 mg of pyribenzamine or benadryl

5 Avoid local therapy Instillations and instrumentation of vagina or urethra lead only to complications

6 In the case of penicillin sensitivity accomplish prophylaxis against all five venereal diseases by using larger doses of aureomycin or chlor amphenicol to insure spirochetocidal effect Give 500 to 1000 mg four times daily for two weeks

7 In the rare instance where for reasons of economy it is necessary to substitute sulfonamide for treatment of gonorrhea prescribe a load ing dose of 2 gm each of sulfamerazine and sulfadiazine with 1 tea spoonful of bicarbonate of soda Thereafter maintain antibiotic levels with oral doses of 0 25 to 0 5 gm each of sulfamerazine and sulfadiazine every four hours night and day for three to five days By contrast with penicillin sulfonamide produces only 50 to 80 per cent of cures toxicity develops in an appreciable number of patients so that urine and blood must be carefully watched during the course of treatment and sensitization occurs in an appreciable number of patients (p 4541)

Continuing Care (Favorable Course)

1 At completion of therapy order patient to report at weekly inter vals for at least a month and at monthly intervals until six months have elapsed since acquisition of infection Take blood tests for serologic reactions at each visit Order the patient to refrain from intercourse for a minimum period of one week even though there is evidence that organisms disappear within a few hours after treatment has been initiated with any of the antibiotics

Continuing Care (Unfavorable Course)

1 Treat the neglected patient who arrives with local complications such as posterior urethritis prostatitis seminal vesiculitis orchitis epididymitis bartholinitis salpingitis pelvic peritonitis or arthritis in the same manner as those with recently acquired infections

2 In gonorrheal bacteremia particularly with endocarditis the severity of the infection requires that excessively large doses be used It is recommended that 600 000 units of procaine penicillin G in aqueous suspension be deposited twice daily for a period of at least two and preferably three weeks Concurrently give supplementary antibiotic therapy prescribing aureomycin or chloramphenicol orally in doses approximating 50 to 100 mg per kilogram of body weight per day (3 5 to 7 gm for average adult weighing 150 pounds) If for any reason this combination of antibiotic cannot be employed substitute sulfonamide For intravenous use give a priming dose of 2 5 gm each

of sodium sulfadiazine and sodium sulfamerazine in 200 cc of diluent preferably physiologic saline 5% dextrose or molar lactate Continue maintenance doses with oral administration of 0 5 gm each of sulfadiazine and sulfamerazine and a teaspoonful of bicarbonate of soda every three four or six hours depending on severity of the disease and patient response Concurrently prescribe antihistamine in daily doses of 200 mg of pyribenzamine or benadryl

3 In the rare instance of keratosis blennorrhagica (p 3257) antihistamine therapy is suggested using benadryl or pyribenzamine in doses of 200 mg daily

4 Effective antibiotic therapy has rendered obsolete gonorrheal vaccine for prophylaxis or treatment instillations into urethra or conjunctival sac of silver proteinates inorganic silver salts potassium permanganate acriflavin proflavin alum etc hyperthermia either generalized or localized estrogen for conversion of infantile vaginal epithelium and the relatively feebly gonococcidal activity of streptomycin

GRANULOMA INGUINALE

Principles of Diagnosis and Therapy

1 The Donovan body (Fig 73 p 475) of granuloma inguinale formerly regarded as a protozoan has been identified as a minute gram negative encapsulated cocco bacillus

2 The newly named Donovania granulomatis is sensitive to aureomycin chloramphenicol and streptomycin

3 Effective use of nontoxic antibiotics has rendered obsolete antimonial therapy with tartar emetic stibosan diramin etc

Practical Management

1 Prescribe 500 mg of aureomycin or chloramphenicol every six hours for ten to fifteen days Aureomycin and chloramphenicol accomplish rapid healing without toxicity or relapse The patient may be treated on an ambulatory basis since it is not required to give parenteral deposits as with streptomycin

2 Streptomycin therapy requires frequent daily injections despite which relapses are fairly frequent Recommended doses are 3 daily injections of 1 gm for ten days or 2 daily injections each of 2 gm for five days

3 Since granuloma inguinale often is associated with other venereal infections (syphilis lymphopathia venereum gonorrhea and chancroid) perform clinical and laboratory examinations for detection of these correlated disorders Make a darkfield examination of local lesion for the spirocheta of syphilis (Fig 7 p 46) urethral spreads for gonococci Frei test for lymphogranuloma venereum (Fig 957 D p 3277) and smears from chancroidal lesions for recognition of H ducreyi (p 2455)

4 Even in the absence of definitive indications of associated venereal

disease give prophylactic therapy The course of aureomycin or chloramphenicol may be relied on to prevent or cure concurrent lymphopathia venereum gonorrhea and chancroid and both drugs also possess spirochetocidal activity However the prevention of syphilis is of such importance that additionally make 10 daily intra muscular deposits of 600 000 units of crystalline procaine penicillin G in aqueous suspension or oil

5 After healing of lesion suggest follow up visits for clinical and serologic examinations for a minimum period of six months If healing is incomplete repeat the primary treatment course The scarring due to local lesions of penis vulva or rectum (Fig 958 p 3277) may require later surgical intervention

6 Obsolete are injections of antimonials including tartar emetic stibosan diramin etc

HABITUAL ABORTION

Defining abortion as the termination of a pregnancy of a duration of 22 weeks or less resulting in a fetus weighing 500 gm or less Javert subdivided patients studied over a 15 year period at the New York Hospital into primary and secondary habitual abortion groups The former were essentially primiparas who had three or more consecutive spontaneous abortions beginning with the first pregnancy in the group of secondary habitual abortions were multiparas who sustained three consecutive spontaneous abortions after delivery of one or more imma ture premature or full term infants The two groups were made up of women who were eight years older than the average clinic patient 25 per cent were primiparas over the age of 35

The incidence of primary habitual abortion was 1 in 300 while the secondary type occurred in 1 to 493

Obstetric complications (including nausea vomiting toxemia of pregnancy and placenta praevia) occurred more often in abortion groups than in controls Gynecologic complications (retroversion myoma uteri double uteri and cervical and endometrial polyps) also were of appreciable higher incidence In the abortion groups there were positive serologic tests for syphilis in 6 per cent hemoglobin values below 70 per cent in 15 per cent and lowered basal metabolic rates in excess of 50 per cent The Rh factor showed no significant variation from expected percentages

When treatment was carried out with bed rest sedation and routine administration of vitamin E and progesterone the numbers of full term pregnancies rose from 26 per cent in the controls to 64 per cent in primary abortion but there was no appreciable change in those with secondary abortion Because of these relatively unsatisfactory results the therapeutic plan of procedure was changed patients were not confined to bed they were not given sedation gynecologic abnor malities were corrected the diet was supplemented with vitamins C

and K and with necessary minerals thyroid extract was prescribed for tho e with a low basal metabolic rate and coitus was restricted throughout the entire pregnancy

With this latter form of rational therapy the percentage of full term infants ro e from 26 in the controls to 80 in the primary group and from 48 to 100 per cent in the secondary group Some patients in the group treated by the rational approach received vitamin E and progesterone but later omission of these alleged specifics resulted in equally satisfactory therapeutic results In consequence the investigators regard these items as no longer a part of present therapy

HERPES SIMPLEX

[Herpes Febrilis Cold Sores Eczema Herpeticum Kaposi s Varicelliform Eruption Acute Herpetic Gingival Stomatitis Aphthous Stomatitis Acute Infectious Gingival Stomatitis]

General Principles of Diagnosis and Therapy

1 Herpes simplex is ordinarily a benign virus infection of the skin (Fig 61 p 388 Fig 70 D p 436) Occasionally however it may be associated with encephalopathy

2 On this account it would appear wise to treat herpes simplex actively using chloramphenicol which is of demonstrable value in herpes zoster (see below)

3 Since there is the possibility that the neurologic complication may be a hyper ensitivity phenomenon additionally order antihistamines such as 200 mg daily of pyribenzamine or benadryl

4 If encephalopathy develops resume antihistamine in massive doses (800 mg daily) try encephalitis vaccine Herpes F strain (Lederle) as in epidemic encephalitis (p 4309) and apply for cortisone to Merck and Co

HERPES ZOSTER

[Shingles]

General Principles of Diagnosis and Therapy

1 Herpes zoster is a painful and occasionally damaging virus infection (Fig 70 A B p 436)

2 The virus seems to be specifically sensitive to chloramphenicol which may be given in daily doses approximating 50 mg per kilogram of body weight per day (2 products every four hours for the average

disease give prophylactic therapy The course of aureomycin or chloramphenicol may be relied on to prevent or cure concurrent lymphopathia venereum gonorrhea and chancroid and both drugs also possess spirochetocidal activity However the prevention of syphilis is of such importance that additionally make 10 daily intra muscular deposits of 600 000 units of crystalline procaine penicillin G in aqueous suspension or oil

5 After healing of lesion suggest follow up visits for clinical and serologic examinations for a minimum period of six months If healing is incomplete repeat the primary treatment course The scarring due to local lesions of penis vulva or rectum (Fig 958 p 3277) may require later surgical intervention

6 Obsolete are injections of antimonials including tartar emetic stibosan diramin etc

HABITUAL ABORTION

Defining abortion as the termination of a preanancy of a duration of 22 weeks or les resulting in a fetus weighing 500 gm or less Javert subdivided patients studied over a 15 year period at the New York Hospital into primary and secondary habitual abortion groups The former were essentially primiparas who had three or more consecutive spontaneous abortions beginning with the first pregnancy in the group of secondary habitual abortions were multiparas who sustained three con ecutive spontaneous abortions after delivery of one or more imma ture premature or full term infants The two groups were made up of women who were eight years older than the average clinic patient 25 per cent were primipara over the age of 35

The incidence of primary habitual abortion was 1 in 300 while the secondary type occurred in 1 to 493

Obstetric complications (including nausea vomiting toxemia of pregnancy and placenta praevia) occurred more often in abortion groups than in controls Gynecologic complications (retroversion myoma uteri double uteri and cervical and endometrial polyps) also were of appreciable higher incidence In the abortion groups there were positive serologic test for syphili in 6 per cent hemoglobin values below 70 per cent in 15 per cent and lowered basal metabolic rates in excess of 50 per cent The Rh factor showed no significant variation from expected percentages

When treatment was carried out with bed rest sedation and routine administration of vitamin E and progesterone the numbers of full term pregnancies ro e from 26 per cent in the controls to 64 per cent in primary abortion but there was no appreciable change in those with secondary abortion Because of these relatively unsatisfactory results the therapeutic plan of procedure was changed patients were not confined to bed they were not given sedation gynecologic abnor malities were corrected the diet was supplemented with vitamins C

2 The presence of positive histoplasmin skin tests in a large per centage of patients with pulmonary calcification and tuberculin nega tivity suggests that histoplasmosis may be widespread

3 Histoplasmin antigen for skin testing is not commercially avail able but may be procured from the United States Public Health Service or from Dr Michael L Furculow of the University of Kansas Hospital Kansas City Kansas

4 Certain shortcomings of histoplasmin skin testing are already apparent Palmer (Public Health Report 61 475 1946) regards the test as of questionable diagnostic value several of his patients with proven histoplasmosis had negative skin tests contrariwise many positive reactors to histoplasmin had no evidences of the disease

5 In addition to errata reported by Palmer cross agglutination occurs in those who are sensitive to actinomycin and blastomycin

6 Despite these deterrents the histoplasmin skin tests is worthy of consideration in the diagnosis of chronic pneumonitis particularly with caseation when tubercle bacilli cannot be incriminated

7 The diagnosis of histoplasmosis has more than academic impor tance Since many of the infected are classified and treated as patients with tuberculosis it is imperative to recognize the etiologic agent inas much as streptomycin therapy of histoplasmosis is completely ineffectual

8 Isolated instances of successful therapy on the contrary have been reported with sulfadiazine promin trivalent and pentavalent antimonials and the new antibiotic bacillomycin

9 Giving daily doses of 4 gm of sulfadiazine for eighty seven days one successful issue has been observed

10 One patient was successfully treated with stibamine glucoside Still another apparently derived benefit from treatment with neosti bosan alternating with stilbamidine

11 Hobart Peimann employed bacillomycin an antibiotic derived from B subtilis (p 4247) Doses of 50 mg were deposited intramuscularly every 6 hours for five to eighteen days The injections caused pain and fever at first but later the febrile response lessened and eventually disappeared

12 A single cure of histoplasmosis was reported following promin therapy

13 There is general agreement that the undernoted drugs are of no value in the treatment of histoplasmosis penicillin streptomycin potassium arsenide arsphenamine acetarsone iodide quinine and atabrine

HODGKIN S DISEASE

[See Blood and Blood forming Organs Neoplasms of]

adult weighing 150 pounds) Favorable effects have been noted also with aureomycin using only 250 to 500 mg every six hours

HEXYLRESORCINOL U S P

[Caprokol Crystoids Anthelmintic]

Hexylresorcinol appears as white or yellowish crystals with faint odor and sharp taste Hexylresorcinol produces the sensation of numbness when placed on the tongue so that it is prescribed in hard pills or capsules

Available Products

Crystoids Anthelmintic (*hexylresorcinol*) (Sharp & Dohme) pills of 0 1 and 0 2 gm strength

Caprokol (*hexylresorcinol*) (Sharp & Dohme) for urinary antisepsis capsules 0 15 gm in 25% solution in olive oil

Therapeutics

Originally introduced as a urinary antiseptic under the name of *caprokol* hexylresorcinol now is rarely used for this purpose *However* it is valuable as an anthelmintic and is first choice in ascariasis trichuriasis and intestinal distomiasis it is second choice in oxyuriasis and uncinariasis

For anthelmintic action hexylresorcinol is preceded by a saline purge the night before administration of the drug In the morning on an empty stomach 1 gm is given for the average adult dose Patients are cautioned against chewing the capsules since the drug is intensely irritating and may produce a local chemical burn Two hours later the saline purge is repeated and three hours after the purge food may be resumed In resistant infection treatment is repeated after an interval of three days

In the treatment of mixed infestations hexylresorcinol is given at least a week before tetrachlorethylene (p 4569)

Toxicology

See p 1895

HISTOPLASMOSIS

General Principles of Diagnosis and Therapy

1 Introduction of histoplasmin for determination of cutaneous sensitivity to the yeast like fungus (Fig 76 F p 487) has greatly stimulated interest in this infection previously thought to be of rare occurrence

Practical Management

Prophylaxis

1 Homologous serum jaundice is more effectually prevented than treated The practitioner must refu e blood donations from individuals who give a frank history of jaundice within the past year or of any ill defined undiagnosed illne s of any duration

2 Unless the need is great avoid use of banked blood

3 Unless the need is great avoid u e of pooled plasma unless it has been irradiated

4 Avoid vaccines containing human erum unless they have been irradiated

5 If it is known that a patient has received contaminated biological fluid initiate prophylactic injections of gamma globulin Introduce 10 cc intramu cularly and repeat at intervals of seven to fourteen days if possible

Immediate Care

1 Carry out the routine suggested for treatment of the infected patient (p 64)

2 Give a full and mixed diet that is palatable to the patient Fat need not be omitted or even reduced

3 Try gamma globulin also for active treatment of patient with frank manifestations of homologous serum hepatitis Inject 10 cc intramus cularly Repeat daily for three or four days if possible

4 Despite lack of evidence of benefit give a probatory course of aureomycin or chloramphenicol the only antibiotics with potential virucidal activity Use large doses up to 100 mg per kilogram per day (7 gm for the average adult weighing 150 pounds) After the priming dose give a similar quantity daily for at least a week or ten days unle the expense is prohibitive

HYALURONIDASE

Hyaluronidase is a mucolytic enzyme representing the spreading factor of Duran Reynals

Available Products

Alidase (Searle) ampuls of 250 viscosity units with diluent of sodium chloride sufficient to make 1 cc of isotonic solution

Hydase Lyophilized (Wyeth) sterile solution containing 150 units

Pharmacology and Therapeutics

Hyaluronidase depolymerizes and decreases the viscosity of intra cellular cement or mucin like substances composed of hyaluronic

HOMOLOGOUS SERUM JAUNDICE

Principles of Diagnosis and Therapy

1 The organism that causes homologous serum jaundice is a hepatogenic and hepatotoxic filtrable virus Parenteral injections of quantities as small as 0 01 to 0 001 cc of infected blood are capable of transmitting the disease from one human to another after an incubation period of forty to one hundred twenty days

2 Homologous serum jaundice bears no etiologic relationship to the spirochetal or leptospiral variety better known as Weil s disease It is distinct from virus hepatitis more commonly termed infectious or catarrhal jaundice whose incubation period is fifteen to thirty four days

3 During World War II yellow fever vaccine made with human serum produced 29 000 infections with 62 fatalities In a group of 200 patients who received transfusions from a blood bank 1 in 200 suffered from homologous serum jaundice The estimated incidence when pooled plasma was employed was 1 in 86

4 Homologous serum jaundice also may be transmitted through mas inoculations when a contaminated syringe imperfectly sterilized is used Of a troop injected with tetanus toxoid from a common syringe 20 per cent developed homologous serum jaundice The problem of the disease therefore is of more than academic interest to the practitioner who uses both blood transfusions and plasma infusions

5 Liver biopsies of patients who recovered showed characteristic cellular changes suggesting toxic hepatitis (p 1963) In fatal instances there were large areas of atrophy with regeneration In convalescence the liver tissues of some patients disclosed evidences of biliary cirrhosis In a few instances the combination of hepatitis cirrhosis and carcinoma was observed

6 Perhaps the largest numbers of those who suffer from homologous serum jaundice present only subclinical evidences of the disease The second largest group also non icteric complain only of malaise anorexia nausea vomiting and low grade fever Studies of liver function in this latter group however reveal distinct changes

7 In its classical form homologous serum jaundice is characterized by icterus first noticed by appearance of bile pigment in urine Most patients are ill for two to three weeks and then experience a prolonged period of asthenia In certain instances the disease terminates fatally with manifestations of acute yellow atrophy (p 1968)

8 At the height of the disease physical findings include fever biliary staining of tissues enlargement of liver and palpable spleen Middle aged females run a stormier course than others and the mortality rate is considerably higher Wounded soldiers appeared to be afflicted more seriously than their more normal comrades in arms

selves) attribute reported benefits to spontaneous variations in blood pressure psychotherapy weight reduction and in the case of those who are institutionalized to the mechanism of escape from environment (p 3754)

8 The highly publicized rice diet of Kempner in our experience is unacceptable to patients and impractical for use in private practice

9 As to various surgical procedures for the control or relief of hypertension *we find ourselves even more set in our views than when* we previously stated that the operative results are not as striking as the enthusiasts would wish The fall in blood pressure is often temporary and may be followed by a return to preoperative levels Headache vertigo and palpitation are often ameliorated out of all proportion to the blood pressure effects In certain spectacular instances fundus changes including papilledema have receded but these happy eventualities are certainly in the minority (p 915)

10 The case for surgical treatment of hypertension has been well delineated by Smithwick (Am J Med 4 744) Unfortunately so far as we are personally concerned statistical studies by the consultant specialist leave much to be desired as best illustrated by an individual case record of a woman referred by us for splanchnicectomy Her blood pre sure readings in our office or in the hospital varied between 130/80 and 260/140 Our rea ons for suggesting surgery were our own inability to control the course of her hypertension a single attack of transitory hemiplegia a single attack of precordial distress undoubtedly due to coronary insufficiency and an attack of paroxysmal cardiac irregularity that ended in forward failure Following a complete and competent two stage splanchnicectomy the patient was hospitalized for a total of four months and incapacitated at home with professional nursing care for an additional eight months involving considerable *expense and sacrifice on the part of husband and family In convalescence* her husband was taught to take her blood pressure and on occasions when she suffered symptoms of orthostatic hypotension he recorded blood pressure levels in the region of 100/80 Two years postoperatively in our office we noted blood pressure levels approximating those seen preoperatively i e 190/130

How shall this patient be reported statistically in the literature? An opponent of operative procedure could well point out that she had blood pressure levels of 130/80 preoperatively and of 190/130 postoperatively indicating continued unfavorable progress proponents of surgery might with equal veracity note levels of 240/160 preoperatively as compared with the husband s reading of 100/80 postoperatively Multiplication of these data a hundredfold with publication of statistical charts and graph does not contribute greatly to solid evaluation of the proposed therapeutic procedure

acid This action permits interstitial spread of various soluble substances ranging from bacteral toxins to antibiotic agents

Currently hyaluronidase is used to facilitate subcutaneous injection of fluid by hypodermoclysis (p 3771) to increase topical efficacy of antibiotics such as penicillin in mucus lined cavities to influence mechanisms responsible for lesions of rheumatic fever (p 4494) and aid fertilization when introduced intravaginally

HYPERTENSION ESSENTIAL

Principles of Diagnosis and Therapy

1 Despite many ingenious therapeutic efforts certain of which have been highly publicized the treatment of essential hypertension remains essentially unchanged so far as the practitioner is concerned Main reliance still is placed on psychotherapy weight reduction sedation hypnosis alterations in the way of life rest cures gentle exercise and abstinence from tobacco (pp 911–914)

2 In the field of specific drug therapy there is now fairly uniform opinion that nitrates nitrites aminophyllin aconite mistletoe watermelon seeds onion extract insulin free pancreatic extracts and other tissue derivatives iodides estrogen and androgen accomplish little of benefit to the patient (p 912)

3 There is now general agreement with our previously stated opinion that use of sulfocyanates is excessively toxic in proportion to their accomplishment (p 912) In a comparison of potassium thiocyanate with a placebo patient complaints increased in approximately 50 per cent and decreased in approximately 33 per cent justifying the conclusion that the drug was unreliable and hazardous

4 There also appears to be unanimity of opinion that the xanthines particularly aminophyllin accomplish little and add considerably to the patient s expense

5 Of older preparations only veratrum viride commends present attention Newly available commercial products assayed by the Craw method provide fairly sustained hypotension through a direct vasodilator mechanism Vertavis (Irwin Neisler) marketed in tablets each containing 10 Craw units may be given in initial doses of 3 to 6 daily and increased to 6 to 10 tablets if no untoward effects become manifest (nausea vomiting)

6 Among newly introduced products which have proven disappointing despite pharmacologic potential are symp itholytic preparations such as tetraethylammonium (Etamon) salts and pri col

7 In dietotherapy efforts have been made to demonstrate the value of regimens which practice restrictions of salt sodium chloride fat and cholesterol In each instance enthusiastic proponents claim specific results whereas the more critical (in which ranks we find our

passive immunity can be produced It is used also to supplement immunizations particularly when immediate protection is required to bridge the gap between injection of antigen (in *artificial active immunity*) and actual production of significant antibody titers

Chemoprophylaxis is practiced with *amebacides* in amebic dysentery with *penicillin* in anthrax diphtheria erysipelas gas gangrene gonorrhea meningococcal infections pneumococcal infections scarlet fever taphylococcal and streptococcal infections and syphilis with *sulfonamides* in chancroid cholera colon bacillus infections gonorrhea granuloma inguinale meningococcal infections and pneumococcal infections with *aureomycin* and/or *chloramphenicol* in cholera colon bacillus infections granuloma inguinale lymphopathia venereum brucellosis whooping cough plague Rocky Mountain spotted fever the salmonelloses the shigelloses typhus fever tsutsugamushi fever and tularemia with *malariacides* in malaria and *trypanosomicides* in African sleeping sickne s

Immunization in Infancy and Childhood

For accomplishment of active immunization practitioners encourage routine inoculation in infancy and childhood

The Special Committee on Child Welfare of the Medical Society of the County of New York has reviewed immunization procedures for the prevention of contagious diseases It recommends the following as a generally satisfactory means of immunization in private practice

Smallpox

1 Vaccinate between third and ninth months provided that the cord has healed and the infant exhibits no manifestations of hypersensitivity such as idiosyncrasy to milk or eggs or atopic dermatitis (infantile eczema)

2 Repeat vaccination pre kindergarten or school pre high school and at any time when there is threat of exposure

3 Prefer the multiple pressure method

4 To these we would add prophylactic u e of antihistamine to combat the rare but grave post vaccinal myeloencephalopathies (p 4307) Give 50 to 200 mg depending on age of pyribenzamine or benadryl daily for three weeks following vaccination

Diphtheria

1 For single diphtheria immunization start injections between the sixth and ninth month of age Give two doses of 1 cc each at monthly intervals of alum precipitated toxoid (p 4302) or three doses at monthly intervals of plain toxoid (p 4206)

2 Inject booster doses of 0 25 cc of toxoid on admission to kindergarten or chool pre high school and to recall immunity on exposure

IMMUNIZATION AND CHEMOPROPHYLAXIS

Immunity is conferred by an attack of an infectious disease (*natural active immunity*) by transfer of antibody from mother to infant (*natural passive immunity*) by stimulation of antibody production through injection of specific antigen (*artificial active immunity*) and by introduction of preformed antibody (*artificial passive immunity*) (p 73-87) Additionally modern science has added the great boon of chemoprophylaxis using specific antibiotics (p 4201)

Natural Active Immunity Natural active immunity is usually permanent It is conferred as the result of a clinical or subclinical bout of the specific infectious disease Natural active immunity follows attacks of chickenpox cholera measles mumps pertussis plague poliomyelitis Rocky Mountain spotted fever and related rickettsioses scarlet fever smallpox typhoid fever typhus fever tsutsugamushi fever tularemia and yellow fever

Patients who give a definitive history of attacks of any of these specific diseases do not require artificial protection Those who have had subclinical attacks in which the diagnosis has not been confirmed clinically or serologically warrant protection on exposure

Natural Passive Immunity Natural passive immunity is conferred by transfer of preformed antibody from mother to infant through placental circulation Natural passive immunity is transitory and lasts at best for a period of six months It is conferred in diphtheria typhoid fever and poliomyelitis

Beyond the age of six months natural passive immunity for diphtheria dissipates Thereafter the child requires diphtheria immunization for development of powerful artificial active immunity

Artificial Active Immunity Artificial active immunity is accomplished by introduction of specific antigen (p 4204) to stimulate manufacture of sufficient specific antibody for purposes of protection

Antigens for induction of artificial active immunity are available in cholera diphtheria virus encephalopathies virus influenza melitensis pertussis plague rabies Rocky Mountain spotted fever scarlet fever smallpox tetanus typhoid fever typhus fever and yellow fever

Routine injection of antigen for production of artificial active immunity is mandatory in diphtheria pertussis smallpox tetanus and typhoid fever On exposure stimulation of artificial active immunity is highly advisable in cholera virus encephalopathies virus influenza plague rabies Rocky Mountain spotted fever tuberculosis tsutsugamushi fever and yellow fever

Artificial Passive Immunity Indications for accomplishment of artificial passive immunity are rapidly shrinking in view of the efficacy of antibiotics Nevertheless there is still an important place in therapeutics for protective antiserums in H influenzae B anthrax tetanus diphtheria gas gangrene *botulism and possibly plague*

Chemoprophylaxis Chemoprophylaxis is of greatest importance in those diseases in which neither artificial active immunity nor artificial

pa sive immunity can be produced It is used also to supplement immunizations particularly when immediate protection is required to bridge the gap between injection of antigen (in *artificial active immunity*) and actual production of significant antibody titers

Chemoprophylaxis is practiced with *amebacides* in amebic dysentery with *penicillin* in anthrax diphtheria erysipelas gas gangrene gonorrhea meningococcal infections pneumococcal infections scarlet fever staphylococcal and streptococcal infections and syphilis with *sulfonamides* in chancroid cholera colon bacillus infections gonorrhea granuloma inguinale meningococcal infections and pneumococcal infections with *aureomycin* and/or *chloramphenicol* in cholera colon bacillus infections granuloma inguinale lymphopathia venereum brucellosis whooping cough plague Rocky Mountain spotted fever the salmonelloses the shigelloses typhus fever tsutsugamushi fever and tularemia with *malariacides* in malaria and *trypanosomicides* in African sleeping sickne s

Immunization in Infancy and Childhood

For accomplishment of active immunization practitioners encourage routine inoculation in infancy and childhood

The Special Committee on Child Welfare of the Medical Society of the County of New York has reviewed immunization procedures for the prevention of contagious diseases It recommends the following as a generally satisfactory means of immunization in private practice

Smallpox

1 Vaccinate between third and ninth months provided that the cord has healed and the infant exhibits no manifestations of hypersensitivity such as idiosyncrasy to milk or eggs or atopic dermatitis (infantile eczema)

2 Repeat vaccination pre kindergarten or school pre high school and at any time when there is threat of exposure

3 Prefer the multiple pressure method

4 To these we would add prophylactic u.e of antihistamine to combat the rare but grave post vaccinal myeloencephalopathies (p 4307) Give 50 to 200 mg depending on age of pyribenzamine or benadryl daily for three weeks following vaccination

Diphtheria

1 For single diphtheria immunization start injections between the sixth and ninth month of age Give two doses of 1 cc each at monthly intervals of alum precipitated toxoid (p 4302) or three doses at monthly intervals of plain toxoid (p 4206)

2 Inject booster doses of 0 25 cc of toxoid on admission to kindergarten or school pre high school and to recall immunity on exposure

Tetanus

1 *Administer tetanus toxoid in the manner of diphtheria toxoid*

2 For booster doses however use doses of 0 5 cc In the event of accident or trauma prefer fluid toxoid since the response to alum precipitated toxoid is not sufficiently prompt for acute need

Pertussis

1 Start immunization at third or fourth month If saline suspension of vaccine is used give 20 billion organisms for the initial deposit follow at monthly intervals by two injections each of 30 billion bacilli to total 80 billion hemophili If alum precipitated vaccine is used give three monthly injections each of 15 billion organisms to total 45 billion hemophili

2 Give booster doses of 20 billion organisms in saline suspension or of 10 billion of alum precipitated vaccine at the third year and again to recall immunity on exposure

Triple Immunization

1 Triple immunization against diphtheria tetanus and pertussis may be given with a single product Reactions are scarcely more severe and immunity levels are not impaired Starting at the age of four months inject combined diphtheria toxoid alum precipitated tetanus toxoid alum precipitated and pertussis vaccine alum precipitated in doses of 1 cc at monthly intervals

2 Whereas some members of the Committee favor triple immunization the method has not yet been officially endorsed by the American Academy of Pediatrics or the Committee on Immunization Procedures of the American Public Health Association

3 Booster injections of 1 cc are suggested at the first birthday For purposes of recall of immunity on exposure to any one of the three infections use the single indicated product i e diphtheria toxoid tetanus toxoid or pertussis vaccine

Measles

1 Inject 2 cc of gamma globulin following direct exposure to measles Passive immunity lasts only three weeks Active immunity of a permanent nature follows modified measles and many instances of so called aborted disease

Author s Method

Our personal preferences for immunization are indicated in the accompanying Time Table

TIME TABLE FOR ACTIVE IMMUNIZATION IN INFANCY AND CHILDHOOD

Age	Prophylactic
3 to 6 months	Smallpox vaccine (p 427) with antihistamine
6 to 12 months	1 cc Diphtheria Toxoid, Tetanus Toxoid Alum Precipitated Whooping Cough Vaccine Combined
2 weeks later	1 cc Whooping Cough Vaccine (p 283)
2 weeks later	Repeat Diphtheria Toxoid, Tetanus Toxoid, Pertussis Vaccine as above
18 to 24 months	Schick test (p 304) Booster of Diphtheria Toxoid, if positive
5 to 6 years (pre-school)	Repeat Diphtheria Toxoid Tetanus Toxoid Pertussis Vaccine as above
6 to 10 years (school and camp)	Typhoid vaccine (p 236) Repeat Smallpox Vaccine and Tetanus 'booster (p 298)
13 to 14 years (high school)	Repeat Smallpox Vaccine Typhoid Vaccine and Tetanus booster

Immunization in Adult Life

Adults who have not received active immunization in infancy and childhood are given the original schedule previously listed There after they as well as those who have had childhood immunizations are entitled to booster doses of typhoid tetanus and diphtheria and to a repetition of smallpox inoculations after three to five year intervals

Immunization on Exposure

On exposure in addition to routine immunizations protection should be afforded adults and children threatened with typhus plague cholera yellow fever malaria amebiasis tularemia Rocky Mountain spotted fever rabies influenza virus and venereal diseases

ACTIVE IMMUNIZATION FOR ADULT

Age 18

If immunized in childhood repeat smallpox vaccine (p 427) typhoid vaccine (p 236) and tetanus 'booster (p 298)

If not immunized, give
1 Typhoid vaccine
2 Smallpox vaccine
3 Diphtheria toxoid tetanus toxoid, pertussis vaccine combined

Every 5 years

Repeat
1 Smallpox vaccine
2 Typhoid booster
3 Tetanus booster

On exposure travel to infected countries or special indications

Repeat above and in addition consider
1 Typhus vaccine (p 375)
2 Plague vaccine (p 322)
3 Cholera vaccine (p 250)
4 Yellow fever vaccine (p 480)
5 Tularemia vaccine (p 326)
6 Rocky Mountain spotted fever vaccine (p 380)
7 Rabies vaccine (p 433)
8 Influenza virus AB vaccine (p 397)

Travelers

An immunization schedule for travelers has been prepared by the Department of National Health and Welfare of Canada These recommendations are applicable equally to citizens of the United States of America

IMMUNIZATION SCHEDULE FOR TRAVELERS*

Country or Region of Destination	Small pox	Diph theria	Ty phoid	Typhus	Cholera	Yellow Fever	Plague
Argentina	x	x	x	x	—	x	—
Australia	x	x	x	x	—	—	—
Belgium	x	x	x	x	—	—	—
Brazil	x	x	x	x	—	x	—
British West Indies	x	x	x	—	—	x	—
British West Africa	x	x	x	x	—	x	—
Chile	x	x	x	—	—	x	—
Colombia	x	x	x	x	—	x	—
China	x	x	x	x	x	—	x
Cuba	x	x	x	x	—	x	—
Egypt	x	x	x	x	x	—	x
England	x	x	—	—	—	—	—
Federated Malay States	x	x	x	x	x	—	x
Formosa	x	x	x	x	x	—	—
France	x	x	x	x	—	—	—
Greece	x	x	x	x	—	—	—
Guatemala	x	x	x	x	—	x	—
India	x	x	x	x	x	—	x
Ireland	x	x	—	—	—	—	—
Italy	x	x	x	x	—	—	—
Indo-China	x	x	x	x	—	—	—
Japan	x	x	x	x	x	—	—
Korea	x	x	x	x	x	—	—
Mexico	x	x	x	x	—	—	—
Netherlands	x	x	x	x	—	—	—
Netherlands East Indies	x	x	x	x	x	—	x
Newfoundland	x	x	—	—	—	—	—
New Zealand	x	x	x	—	—	—	—
Norway	x	x	x	x	—	—	—
Peru	x	x	x	x	—	x	—
Portugal	x	x	x	x	—	—	—
Russia	x	x	x	x	—	—	—
Siam	x	x	x	x	x	—	x
Straits Settlement	x	x	x	x	x	—	x
South Africa	x	x	x	x	—	—	—
Sweden	x	x	x	x	—	—	—

Only schick positive personnel who give a negative control test should be immunized

E L. Davey M D Department of National Health and Welfare Ottawa Canada Immunization procedures recommended for foreign travel Canad M A J 58 77-79 1948

Combined Immunity and Chemoprophylaxis The ingenious practitioner combines the principles of immunization and chemoprophylaxis in order to protect his patient against a wide variety of microbic invasions as presented in the accompanying chart (p 4367)

PRACTICAL PREVENTIVE MEDICINE IN INFECTIOUS DISEASES

Disease	Natural Active Immunity	Natural Passive Immunity	Artificial Active Immunity	Artificial Passive Immunity	Chemoprophylaxis
Amebiasis	0	0	0	0	Amebacides
Anthrax	0	0	0	Feeble	Penicillin
Chancroid	0	0	0	0	Sulfonamide aureomycin, chloramphenicol
Chickenpox	+	0	0	0	0
Cholera	+	0	+	0	Sulfonamide aureomycin or chloramphenicol
Coli infection	0	0	0	0	Sulfonamide aureomycin or chloramphenicol
Diphtheria	0	6 mos.	+	+	Penicillin
Encephalopathies	0	0	Try Jap B Equine St. Louis Herpes F Vaccines	0	0
Erysipelas	0	0	0	0	Penicillin, sulfonamide
Gas Gangrene	0	0	0	+	Penicillin
Gonorrhea	0	0	0	0	Penicillin, sulfonamide
Granuloma Inguinale	0	0	0	0	Aureomycin/chloram phenicol
Influenza (Virus)	0	0	+	0	0
Lymphopathia Venereum	0	0	0	0	Aureomycin/chloram phenicol
Malaria	0	0	0	0	Malaricides (p 4397)
Measles	+	0	0	+	0
Melitensis infection	0	0	Feeble	0	Aureomycin/chloram phenicol
Meningococcus infection	0	0	0	+	Penicillin, sulfonamide
Mumps	+	0	0	0	0
Pertussis	+	0	+	0	Aureomycin/chloram phenicol
Plague	+	0	+	0	Sulfonamide aureomycin/ chloramphenicol
Pneumococcus infection	0	0	0	Feeble	Penicillin, sulfonamide
Poliomyelitis	0	6 mos.	0	0	0
Rabies	0	0	+	+	Try aureomycin/chloram phenicol
Rocky Mountain spotted fever	0	+	1 yr	0	Aureomycin/chloram phenicol
Salmonellosis	0	0	Feeble	0	Aureomycin/chloram phenicol
Scarlet fever	+	0	Feeble	Feeble	Penicillin
Shigellosis	0	0	Feeble	0	Aureomycin/chloram phenicol
Smallpox	+	0	+	0	0
Staphylococcus infection	0	0	Feeble	0	Penicillin, sulfonamide
Streptococcus infection	0	0	0	Feeble	Penicillin, sulfonamide
Syphilis	0	0	0	0	Penicillin
Tetanus	0	0	+	+	Penicillin
Trypanosomiasis	0	0	0	0	Trypanosomicides (p 4594)
Tsutsugamushi fever	+	0	Feeble	0	Aureomycin/chloram phenicol
Tuberculosis	0	0	BCG	0	0

PRACTICAL PREVENTIVE MEDICINE IN INFECTIOUS DISEASES (Continued)

Disease	Natural Active Immunity	Natural Passive Immunity	Artificial Active Immunity	Artificial Passive Immunity	Chemoprophylaxis
Tularemia	+	0	Feeble	0	Aureomycin/chloramphenicol
Typhoid fever	+	6 mos	+	0	Chloramphenicol
Typhus fever	+	0	+	0	Aureomycin/chloramphenicol
Yellow fever	+	0	+	0	0

INCLUSION CONJUNCTIVITIS

[Inclusion Blennorrhea Swimming Pool Conjunctivitis Paratrachoma]

General Principles of Diagnosis and Therapy

1 Inclusion conjunctivitis is a viral infection that is particularly damaging to newborn In the adult it is apt to occur in those who use swimming pools where the virus may be transmitted from genitals to eye It is possible that the etiologic organism is related to that which causes lymphopathia venereum (p 4391)

2 Whereas moderate success has followed sulfonamide therapy (p 1623) local and systemic administrations of aureomycin possess greater potential at lesser hazard

3 Specifically anoint lids with aureomycin hydrochloride ointment (3%) Instill into each conjunctival sac at two hour intervals 2 to 4 drops of aureomycin borate ophthalmic solution made by dissolving contents of a vial containing 25 mg of antibiotic in 5 cc of diluent supplied by manufacturer This solution is stable at refrigerator temperatures for two days

4 Supplement local and topical therapy by oral administration of 50 mg of aureomycin per kilogram per day (2 capsules every six hours for the average adult weighing 150 pounds)

INFECTIOUS LEUKOPENIA

Regard infectious leukopenia as a variant of infectious mononucleosis and manage the illness in similar manner (p 4369)

INFECTIOUS LYMPHOCYTOSIS

Regard infectious lymphocytosis as a variant of infectious mononucleosis and manage the illness in like manner (p 4369)

INFECTIOUS MONONUCLEOSIS

[Glandular Fever]

Principles of Diagnosis and Therapy

1 Infectious mononucleosis is a viremia (p 466) whose diagnosis is established definitively by the characteristic blood picture (Fig 71 p 469) and by development of heterophile agglutination (Paul Bunnell test)

2 While the course of infectious mononucleosis is invariably benign the chronicity of symptoms may be exhausting to the patient and dis turbing to the physician On a few occasions changes have been noted in electrocardiograms In a group of 206 patients Isaacs reported that fifty three had persistent symptoms for from three months to four years or longer

3 The development of a false positive Wassermann reaction (p 337) in the course of infectious mononucleosis is another disturbing feature of the syndrome Confusion in diagnosis is increased if the misleading serologic reaction is accompanied by clinical manifestations suggestive of secondary syphilis such as lymphadenitis and a scarlatiniform eruption

4 Recent studies reveal that hepatitis almost identical with that seen in viral hepatitis is present in infectious mononucleosis In nine teen consecutive patients suffering from infectious mononucleosis without jaundice varying degrees of hepatic dysfunction were revealed by serial cephalin cholesterol flocculation and sulfobromophthalein excretion tests The duration of hepatic involvement ranged from two weeks to five months and there was usually enlargement and tender ness of the liver during this period

5 Successful but inconsistent results have been obtained by use of aureomycin and chloramphenicol in the treatment of infectious mono nucleosis It is suggested that patients be given 60 to 100 mg per kilo gram of body weight per day (4 products every three to six hours for the average adult weighing 150 pounds)

6 The use of anti infective agents may be supplemented with injec tions of gamma globulin as in viral hepatitis particularly in the early phases of the infection intramuscular injections of 4 to 8 cc are strongly recommended for children and 10 to 20 cc for the adult

7 In the chronic infectious phases of mononucleosis Isaacs found that residual symptoms responded to treatment with adrenal cortical extract

INFECTIOUS POLYNEURITIS

[Guillain Barre Syndrome Landry s Paralysis
Encephalomyeloradiculitis Infectious Neuronitis Acute Polyneuritis with Facial Diplegia]

1 Infectious polyneuritis is a viremia characterized by neurologic signs referable to peripheral spinal and cranial nerves The illness

usually is most prevalent in the cold months of the year and may la t for several weeks or several years The mortality rate approximates 20 per cent

2 Infectious polyneuritis is accompanied by a mild polymorphonuclear leukocytosis Cerebrospinal fluid findings include increased pressure normal cells and greatly increased amounts of protein which may reach 800 mg per 100 cc (albuminocytologic dissociation)

3 In view of the prolonged cour_e of the disea e and its high mortality rate treatment with the only effective antibiotic virucides aureomycin and chloramphenicol merits trial in large doses (100 mg per kilogram per day)

INFLUENZA (HEMOPHILUS) INFECTION

Principles of Diagnosis and Therapy

1 Hemophilus influenzae is a frequent etiologic agent in upper respiratory infections nasopharyngitis otitis mastoiditis otogenic and rhinogenic meningitis laryngotracheobronchitis acute pneumonitis subacute bacterial endocarditis and conjunctiviti

2 Most H influenzal infections are self limited but some such as laryngotracheobronchitis subacute bacterial endocarditis and meningitis carried high pre treatment mortality rates

3 Except in subacute bacterial endocarditis and meningitis the bacteriologic diagnosis of Hemophilus influenzal invasion is rarely made From blood and infected cerebrospinal fluid however the organism may be identified a_ a minute pleomorphic gram negative cocco bacillus (p 285)

4 Invasions due to Hemophilus influenzae require differentiation from those due to influenza virus (p 4372) For the viral infection prophylactic vaccination is of proven efficacy but the organism is antibiotic resistant

By contrast in Hemophilus influenzae infections influenza bacterial vaccine (Kirk Lilly Parke Davis Pitman Moore Sharp & Dohme Sherman Upjohn) is not recommended but active therapy is successfully accomplished by several antibiotics (aureomycin chloramphenicol streptomycin and soluble _ulfonamides)

5 In addition to antibiotics Hemophilus influenzae al o respond to specific heterologous antibacterial serum A refined and concentrated antihemophilus influenza type B rabbit serum is commercially available (Squibb) Vials containing 25 mg of precipitable antibody nitrogen are marketed with diluted serum for skin and ophthalmic testing After desensitization if necessary the contents of 1 to 4 vials (diluted to 25 or 100 cc with physiologic saline _olution) may be introduced by continuous intravenous drip Serum therapy may be repeated after twenty four and/or thirty six hours if required

Practical Management

Immediate Care

1 In the management of invasions of lesser gravity symptomatic therapy usually suffice (p 67) More serious inflammatory processes require intensive and combined anti infective therapy preferably under institutional circumstances Particularly is this precaution required in laryngo tracheobronchitis subacute bacterial endocarditis and men ingitis

2 On admission of the severely infected patient obtain blood spinal fluid or sputum for culture typing of the isolated organism and testing against available antibiotics and immune serums

3 Summon consultant otolaryngologist to survey accessory nasal sinuses middle ears mastoid cells and adjacent blood sinuses for evidences of feeding focal inflammation If indicated consider trache otomy (p 3958) drainage of accessory nasal sinuses exenteration of mastoid cells or ligation of infected venous sinuses

4 As first choice in the antibiotic treatment of Hemophilus influenzae infections prescribe aureomycin or chloramphenicol preferably the former Depending on severity of infection and patient resistance give priming dose of 50 to 100 mg per kilogram of body weight (3 to 7 gm for average adult weighing 150 pounds) Suggest that 2 products be swallowed every few minutes with fruit juice tea milk ice cream or soup to allay gastric irritability

5 If stomach is intolerant of aureomycin substitute chloramphenicol in larger dosage

6 If neither antibiotic is tolerated orally resort to a rectal infusion improvised by dissolving contents of capsules in physiologic saline Use double to quadruple doses Warm and slowly introduce with a male catheter meanwhile holding buttocks firmly together

7 As an alternative to rectal administration in those with gastric intolerance inject aureomycin hydrochloride intravenously Give at least 100 mg dissolved in diluent provided by manufacturer Repeat at six to eight hour intervals until antibiotic is tolerated orally or rectally

8 Reserve streptomycin for those who cannot take aureomycin or chloramphenicol Make a priming intramuscular deposit of 1 to 2 gm

9 Depending on patient reaction start daily maintenance doses of streptomycin within twelve to twenty four hours Give an amount equal to priming dose in 2 divided portions at approximately 12 hour intervals

Continuing Care (Favorable Course)

1 Maintain antibiotic levels with aureomycin or chloramphenicol or with streptomycin as indicated above

2 If streptomycin is substituted start antihistamine prescribing daily 200 mg of pyribenzamine or benadryl in 4 divided doses Continue for at least two weeks after introduction of the last dose of antibiotic

Continuing Care (Unfavorable Course)

1 With evidences of meningitis respiratory obstruction overwhelming toxemia or bacteremia supplement aureomycin/chloramphenicol or streptomycin with soluble sulfonamide Introduce intravenously 75 mg per kilogram of body weight (16 cc of 5% solution for each 25 lbs in infancy) Use equal parts of sodium sulfadiazine and sodium sulfamerazine (p 4546)

2 Depending on patient response start maintenance doses of sulfonamide eight twelve or twenty four hours after introduction of priming amount Give a dose equal to priming dose divided in 2 or 3 portions at 8 or 12 hour intervals

3 If antihistamine has not yet been started prescribe doses as above concurrently with sulfonamide

4 In graver infections (obstructive laryngotracheobronchitis subacute bacterial endocarditis or meningitis) establish an intravenous drip Alternately deliver aureomycin hydrochloride soluble sulfonamide and antihistamine (5 cc of 1% benadryl)

5 Reserve antihemophilus influenza type B hyperimmune rabbit serum for desperation use After test for sensitivity and desensitization when necessary add serum therapy to the combination of aureomycin/chloramphenicol or streptomycin with soluble sulfonamide and antihistamine

6 Intrathecal therapy in Hemophilus influenzae meningitis no longer appears warranted (Hoyne *J A M A 136 597 1948*) The spinal puncture is physically and psychologically a trial to the already depleted patient intrathecal introduction of foreign substance produces an aseptic meningitis with pleocytosis and subsequent manifestations of increased intraspinal pressure and treatment results in those who receive antibiotic and antiserum parenterally are as satisfactory as in those who have had additional intrathecal introduction of therapeutic agents (p 4409)

INFLUENZA VIRUS INFECTIONS

Principles of Diagnosis and Therapy

1 Differentiate influenza virus infections from those due to Hemophilus influenzae (p 4371)

2 Influenza virus infections resistant to currently available antibiotics may be successfully prevented by induction of a transitory artificial active immunity with influenza virus vaccine Types A and B (Lederle Lilly National Drug Parke Davis Pitman Moore Sharp & Dohme Squibb)

3 Influenza virus vaccines are harvested from allantoic fluid of infected chick embryos The product is then formalin killed after which it is refined and concentrated

4 Because of unpreventable contamination of vaccine with egg

protein withhold immunization of those who give a history of hyper sensitivity to chicken or egg proteins (p 4329)

5 Make skin test of prospective recipients of vaccine with 1 10 dilu tion of the commercial preparation about to be used Reject those who give an immediate positive response

Practical Management

1 Advocate biannual immunization with influenza virus vaccine provided that the patient has neither a history nor skin test suggesting hypersensitivity to chicken or egg protein In the presence of a serious epidemic (p 396) cautiously introduce vaccine by multiple intra cutaneous injections

2 Although single 1 cc doses of vaccine are recommended (Coun cil on Influenza of the United States Army J A M A 124 982 1944) it is our custom to give 2 doses each of 0 5 cc at 24 or 48 hour intervals Immunity is established somewhere between the eighth and eleventh days It persists at an effective level for a minimum period of four months In the presence of an outbreak of epidemic influenza virus infection booster doses of 0 5 cc are advised injected sub- or intra cutaneously

3 Since widespread availability of newer anti infective agents there has been fortunately no serious epidemic or virus influenza (p 396) In the event that epidemic virus influenza again attacks probatory anti infective therapy with aureomycin or chloramphenicol is suggested as in graver H influenzal invasions

4 Under experimental investigation and not commercially avail able are newer antibiotics including LL 47 and pectin the latter a derivative of apples

INSECTICIDES AND RATICIDES

The importance of insecticides and raticides is emphasized by the following listing of microbic infections transmitted to man by lice fleas flies mosquitoes mites and ticks (Cf Table 2 p 42)

Bacterial Infections Typhoid fever salmonelloses shigelloses bubonic plague tularemia anthrax

Treponematoses Relapsing fever yaws

Rickettsemias Louse borne typhus fever tsutsugamushi diseases Rocky Mountain spotted fever

Viremias Yellow fever dengue verruca peruana sandfly fever St Louis encephalitis equine encephalomyelitis

Protozoal Infections Malaria leishmaniasis onchocercosis

Helminthiasis Filariasis trypanosomiasis loaiasis

Additionally the rat and its fleas disseminate rat bite fever plague and endemic typhus fever

While the problem of pest control is the province of the public health officer the practitioner must be aware of progress made in the control

SYMPTOMS AND TREATMENT OF POISONINGS DUE TO INSECTICIDES AND RODENTICIDES

INSECTICIDES Product	Portal of Entry			Symptoms	Estimated Lethal Dose for 60-kg Man	Treatment
	Mouth	Lung	Skin			
Lethanes Thanite (Aliphatic Thiocyanates)	X			Deep depression cyanosis dyspnea and tonic convulsions Rapid circulatory collapse and death	24–120 cc of 50% kerosene solution	Gastric lavage and symptomatic
DDT (Dichloro diphenyltri chloroethane)	X	X	X	Tremors progressing to tonic and clonic convulsions Ventricular fibrillation	Unknown Possibly 30 gm	Gastric lavage Anticonvulsant drugs (phenobarbital) *Epinephrine is contraindicated*
Methoxychlor (Dimethoxydiphenyl trichloroethane)	X			Usually limited to depression Tremor *may be noted in chronic poisoning*	400 to 450 gm	Removal of insecticide from stomach and intestinal tract *Oil cathartics should be avoided*
TDE (DDD) Dichlorodiphenyl dichloroethane)	Y		X	Lethargy	240 to 300 gm	Removal of insecticide from stomach and intestinal tract *Oil cathartics should be avoided*
Chlordane (Octachloromethano tetrahydoindane)	X	X	X	Irritability of central nervous system Convulsions followed by depression This cycle may be repeated several times	6 to 60 gm	Removal of insecticide from stomach and intestinal tract Symptomatic
Benzene Hexachloride (Mixtures of *alpha beta gamma* and *delta* isomers)	X	X	X	Hyperexcitability and convulsions caused by *alpha* and *gamma* isomers Depressant effect of *delta* isomer tends to counteract the action of the *alpha* and *gamma* isomers	About 30 gm of technical benzene hexachloride containing 15% *gamma* isomer	Follow general treatment plan given for DDT

Toxaphene (Chlorinated camphene)	X	X	X	Similar to tho e elicited by toxic do es of camphor Epileptiform convulsions	2 to 7 gm	Evacuation of stomach and intestinal tract Anticonvulsant drugs (bromides or phenobarbital)
Organic Phosphates (Tetra ethyl pyrophosphate and Parathion)	X	X	X	Muscarine effect (lacrimation salivation sweating nausea vomiting diarrhea bronchiolar constriction miosis and disturbance of vision) Nicotine effect (flushing of skin throbbing in head heart block muscle tremor)	12 to 20 mg	Evacuation of stomach and intestinal tract Atropine 0 5 to 1 0 mg Peripheral muscular depressants (magnesium sulfate intravenously) Calcium gluconate should be available in case of overdosage of magnesium sulfate
RODENTICIDES						
1080 (Sodium Fluoroacetate)	X			Epileptiform convulsions Pulsus alternans followed by premature systoles and ventricular fibrillation	300 mg	Immediate emesis and gastric lavage Oral magnesium sulfate Anticonvulsant drugs (barbiturate) Complete rest If ventricular fibrillation occurs intravenous injection of 5 cc of a 1 % solution of procaine hydrochloride may restore an organized heartbeat
Antu (*Alpha* naphthylthiourea)	X			Sharp drop in body temperature Increased blood sugar levels Pleural effusion, torpor dy pnea and death	Possibly 300 gm (based on data calculated for *Macaca mulata* monkey)	Prompt evacuation of stomach followed by treatment for econdary shock Oxygen under positive pressure Massive intraperitoneal doses of cy teine up to 2000 mg /kg

of vectors in infectious di ease Through u.e of new in.ecticides it i possible today (1949) to break within a few days or weeks epidemics of human disease such as louse borne typhus malaria dengue sand fly fever and a number of other important diseases (Knipling)

Insecticides

An admittedly bewildering array of new insecticides has appeared on the market The practitioner is required to have some familiarity with these products to prevent dissemination of insect borne di ea es when called to treat his individual patient afflicted with a vector transmitted illness

ROSTER OF INSECTICIDES

OF VEGETABLE ORIGIN

Derris (Rotenone)
A mild irritant to skin and conjunctiva Used for spraying crops Not for application to humans or their premises

Pyrethrum Flowers (Insect Powder)
Insecticide especially for bed bugs and roaches Used in spray bomb (Flit) and with DDT in U S Army Aerosol Pyrethrum Bomb Mammalian toxicity low

Nicotine
Too toxic for u e on humans or their premises

SYNTHETICS

Lethane (Aliphatic thiocyanates)
Too toxic for use on humans or their premises

CHLORINATED HYDROCARBONS

DDT
See text

Methoxychlor (C_1 H $_5Cl_3O$ $_2$)
Less acute toxicity for man and most insects than DDT but posse ses danger of chronic toxic nephropathy

TDE ($C_{14}H_{10}Cl_4$) **Rhothane**
Danger of chronic toxicity for liver and adrenals

Chlordane
Several times a toxic to houseflies and roaches as DDT Also useful against ants chiggers fleas mosquitoes boll weevil and plum and squa h bugs Oral use as toxic as DDT but action is less lasting Used primarily for arge scale pest control particularly grasshoppers

Benzene Hexachloride *(666 Gammexene)*
Has twice oral toxicity of DDT hepatotoxic but effective on livestock against lice ticks boll weevils gras hopper and wireworms

Toxaphene (Chlorinated Camphene)
Has four times oral toxicity of DDT U ed for cotton pests Not for use on humans or their premises

ORGANIC PHOSPHATES

Hexaethyl Tetraphosphate and Tetraethyl Pyrophosphate
Thirty five times oral toxicity of DDT Used externally for roaches flies insects and aphid

Parathion (E 605)
Seventy times oral toxicity of DDT Has garlic like odor U ed only for DDT resistant insects

Insect Repellents

The United States Army has chosen the undernoted formula as the currently best available insect repellent

Dimethyl Phthalate	36 0
Putger s 612 (2-ethyl 1 3 hexanediol)	12 0
Indalone	12 0

Directions Apply to the skin by shaking a few drops in one hand Then rub hands together and smear over exposed parts Avoid mouth and eyes Use also to impregnate clothing Protective action lasts for one to eight hours again t mosquitoes biting flies chiggers ticks fleas gnats sandflies midges and mites

Practical Applications Practical applications of knowledge of insect repellents and insecticides are summarized in the following chart

THERAPEUTICS OF INSECT REPELLENTS INSECTICIDES AND RATICIDES

Indication	Suggested Preparation
Mosquito repellent	U S Army formula
Mosquito larvicide	DDT larvicide powder
Mosquitocide	DDT spray or bomb
Mite repellent	U S Army insect repellent
Miticide	DDT spray or bomb
Chiggers	DDT powder (1 to 5%) or 10% louse powder
Lice	DDT 1 to 5% powder or 10% louse powder
Scabies	See Scabicides (p 4514)
Ticks	DDT powder (10%) or 5% solution in kerosene
Fleas	10% powder or 5% solution in kerosene
Houseflies biting flies roaches gnats bed bugs ants	10% powder bomb or 5% solution in kerosene
Rats	ANTU

Accidental ingestion of insecticides and absorption of the more toxic through the unbroken skin may produce serious and even fatal con sequences (p 4375)

IODIDE

The history of the use of iodide as an anti infective agent is a series of mystifying disappointments Successively tried as bactericide spiro cheticide and fungicide iodide therapy is bewilderingly inconsistent On rare occasions it is specifically successful most often it is unsuc cessful and occasionally it appears harmful As yet these opposed and contradictory results defy explanation

Available Products

Inorganic Salts
Sodium Iodide U S P prefer potassium iodide
Potassium Iodide U S P use saturated solution

Solution of Potassium Iodide N F Preparation of choice each cc contains 1 gm of KI
Syrup of Hydriodic Acid U S P contains 1 4% hydriodic acid prefer potassium iodide
Syrup of Ferrous Iodide U S P prefer potassium iodide
Organic Iodides
Calcium Iodobehenate (Sajodin) contains 23 5% iodide no advantage over inexpensive inorganic salt
Iodostarine contains 47 5% iodide no advantage over inexpensive inorganic salt
Oridine contains 24% iodide no advantage over inexpensive inorganic salt
Iodide Oils (for roentgenography)

Pharmacology

Iodide is rapidly absorbed and diffuses mostly to extracellular fluids It concentrates in the blood in a proportion approximating 3 to 20 micrograms per 100 cc Most iodide is found in skin hair and mu cles though some is stored in the thyroid gland as thyroxin Excretion occurs mostly through urine with les er quantities in saliva and bronchial mucus

Therapeutics

The only demonstrably effective use of iodide as an anti infective agent is resolution of the rarely observed gumma of tertiary syphilis (Fig 49 G and H p 338) To place any confidence in iodide otherwise as an antisyphilitic is a grievous error since it is not comparable to penicillin or the arsenicals (p 4554)

Iodides are extensively employed in the treatment of fungus infection such as actinomycosis blastomycosis sporotrichosis torulosis aspergillosis coccidioidomycosis moniliasis geotrichosis etc Whatever is accomplished in these diseases certain it is that iodides are not specifically fungicidal Most authorities agree that given before vaccine desensitization iodide therapy of the fungus diseases may produce exacerbation of symptoms Given after desensitization those with most experience in the treatment of fungus infections place considerable confidence in iodide therapy (p 4255)

Previously regarded as contraindicated in tuberculosis due to its tendency to produce ulceration and dissemination of lesions iodide therapy is being reinvestigated as an adjunct to antibiotic treatment with the streptomycins

Antitherapeutic Devices

The symptoms of iodism are elsewhere described (p 612) Even to superficial examination iodism bears a considerable similarity to syndromes of acute histamine type hypersensitivity (p 4167) Additionally it has been noted that iodide is capable of producing chronic tuberculin type hypersensitivity manifestations (p 4169)

The pathogenesis of iodide in hypersensitivity reactions together with clinical observations that iodide therapy may cause exacerbation of symptoms in fungus infections tuberculosis and leprosy suggest that iodide has some as yet not clearly demonstrable role in the pro duction of allergic manifestations When this presently mysterious par ticipation has been clarified it may be possible to evaluate iodide therapy with more accuracy and administer the drug to the benefit and not the detriment of the patient Until that time iodide therapy must be undertaken tentatively at all times with due regard to the possibility of producing exacerbation of clinical manifestations

ISONORIN SULFATE N N R

I onorin sulfate is chemically related to isuprel Its formula is 1 (3 4 dihydroxyphenyl) 2 i opropylaminoethanol 1 sulfate

Available Preparations

Tablets Isonorin (C D Smith) 10 mg
Solution Isonorin (C D Smith) (1 200) for oral inhalation

Pharmacology and Therapeutics

Known in Europe under the trade names of aludrine isonorin is identical in its activities to isuprel (q v)

ISOPENTAQUINE OXALATE

Isopentaquine oxalate (8 [4 isopropylamino 1 methylbutylamino] 6 methoxy quinoline) SN 13 274 N N R is a malaricide under investiga tion particularly for combined use with quinine in the treatment of relapsing vivax infections (p 4398)

Available Products

Tablets 10 mg For investigational use only

Therapeutics

In the treatment of relapsing vivax give 10 mg thrice daily for two weeks together with 0 6 gm quinine sulfate

In these small doses i opentaquine has no toxicity The combination with quinine is almost 100 per cent effective excelling even chloro quine and chlorguanide

ISUPREL N N R

Isuprel is a newly prepared adrenergen with many times the activity of epinephrine in combating bronchospasm It exhibits considerably less pressor action so that it is ideally suited for the asthmatic who suffers from bronchospasm and seeks relief without pharmacologically induced hypertension (p 4270)

Available Preparations

Isuprel Tablets (Winthrop) 10 or 15 mg for sublingual administration
Isuprel Solution (Winthrop) (1 200) for oral inhalation

Pharmacology and Therapeutics

Isuprel chemically is 1 (3 4 dihydroxyphenyl) 2 isopropylamino ethanol It is closely related to *isonorin* Taken sublingually inhaled intranasally in 1 200 solution sprayed by a simple hand bulb nebulizer or preferably with oxygen aerosol absorption is rapid and relief is afforded in one to three minutes In the more severe attack isuprel must be repeated after three or four hours The drug should not be administered simultaneously with epinephrine since both substances are pharmacologically related

Side effects of clinically effective doses of isuprel are negligible

JAUNDICE

See Homologous Serum Jaundice Spirochetal Jaundice and Virus Hepatitis

KLEBSIELLOSIS

[Klebsiella Pneumoniae (Friedlander Bacillus) Infections Bacillus Mucosus Capsulatus Infections]

Principles of Diagnosis and Therapy

1 Friedlander s bacillus mucosus capsulatus is a gram negative organism which produces characteristically large mucoid capsules (p 328)

2 Klebsiellas may produce localized infections of upper respiratory passages eye or ear they may invade the blood stream and give rise to bacteremia they may cause a virulent and formerly treatment resistant pneumonitis (pp 2176 2192) and they may travel from respiratory passages to meninges and inaugurate otogenic or rhinogenic meningitis (pp 2128 2148)

3 The diagnosis is suggested clinically by the tenacious character

of exudate or sputum Bacteriologically the organism is identified through its morphologic appearance and cultural characteristics

4 Klebsiellas are insensitive to sulfonamide and penicillin but extremely sensitive to streptomycin aureomycin and chloramphenicol

5 Closely allied to Kl pneumoniae are Kl ozenae and Kl rhinoscleromatis In the presence of infection with either sub-variety therapy is conducted along the same lines as for inva ions with Kl pneumoniae

6 Obsolete is klebsiellosis vaccine commercially available but never of proven clinical value

Practical Management

Immediate Care

1 Because of high infectivity of klebsiellosis institute measures for treatment of the infected patient (p 67)

2 Pre cribe priming dose of aureomycin or chloramphenicol approximating 50 mg per kilogram of body weight (3 5 gm for average adult weighing 150 lbs) To prevent gastric irritation give 1 or 2 capsules every few minutes with a large quantity of milk ice cream fruit juice soup tea or cream cheese

3 Start maintenance doses of antibiotic within six to eight hours after full amount of priming dose has been ingested Give same quantity for daily dose as was prescribed for priming dose but divide into four equal portions taken at approximately six hour intervals

Continuing Care (Unfavorable Course)

1 If stomach is intolerant of either aureomycin or chloramphenicol substitute opposite number Give chloramphenicol in slightly larger doses than were suggested for aureomycin

2 If stomach is tolerant increase daily dose to 100 mg per kg (7 gm for 150 pound adult)

3 If neither antibiotic is tolerated deposit streptomycin intramuscularly in initial priming dose of 1 gm Follow by 0 5 gm every six or eight hours as indicated

4 Since klebsiellas are often secondary invaders combined antibiotic therapy is recommended in virulent and resistant infections More effectively to cover the bacterial spectrum supplement aureomycin chloramphenicol or streptomycin with penicillin using intramuscular deposits of 600 000 units of procaine penicillin G in aqueous suspension for priming and daily maintenance doses

5 Concurrently with combined antibiotic order daily oral doses of antihistamine using 200 mg of pyribenzamine or benadryl for prophylaxis of hyper ensitivity reactions (p 4212) Continue for two weeks after last do e of antibiotic

6 Keep sulfonamides in re erve for particularly resistant infection continue penicillin and either aureomycin chloramphenicol or streptomycin and add soluble sulfonamide Give a priming dose of 2 gm each of sulfadiazine and sulfamerazine with 4 gm of sodium bicar

bonate Continue with maintenance doses of 0 5 gm each every four or six hours as required If stomach is intolerant give intravenous priming dose of 2 5 gm each of sodium sulfadiazine and sodium sulfamerazine in 200 cc of diluent preferably molar lactate

7 Summon consultant otolaryngologist particularly in cases of meningitis Ascertain whether surgical intervention may not be additionally required Particularly with bacteremia look for evidences of mastoiditis and/or sinus thrombosis Prepare for mastoidectomy and/or vein ligation if indicated

KOCH WEEKS CONJUNCTIVITIS

(Pink Eye)

General Principles of Diagnosis and Therapy

1 The organism that produces pink eye (p 1621) is a slim gram negative rod that is sensitive to sulfonamide and aureomycin

2 In view of the lesser threat of the latter it is suggested that treatment be conducted locally and systemically with the newer antibiotic

3 Anoint lids and conjunctivae with 3% aureomycin hydrochloride ointment Instill into each eye 2 to 4 drops at two hour intervals of aureomycin ophthalmic solution prepared by adding 5 cc of diluent supplied by the manufacturer to the vial containing 25 mg of antibiotic Keep this solution in the refrigerator where it remains stable for two days

4 If symptoms are severe or refractory to local therapy supplement with oral doses of aureomycin hydrochloride giving 50 mg per kilogram of body weight per day (2 capsules of 250 mg each every six hours for the average adult weighing 150 pounds)

LABORATORY PROCEDURES SIMPLIFIED

The commercial introduction of several ingenious laboratory aids has simplified the detection in body fluids of albumin sugar acetone and occult blood The tests are economical and sufficiently accurate for all clinical purposes they may be performed by the practitioner in his office laboratory or at the bedside they can be taught the patient for home testing

Albutest

(Ames Company Elkhart Ind)

The tablet method for the qualitative detection of albumin in urine is performed as follows

1 Dissolve 1 Albutest reagent tablet in 4 cc (1 teaspoonful) of water

2 Place 1 cc of urine in a test tube

3 Slant the test tube at a 45° angle

4 Down side of tube slowly deliver 1 cc of reagent

5 In presence of albuminuria (p 3672) a white cloudy ring forms at juncture of fluids The quantity of albumin may be approximated by comparison with standard

Clinitest for Urine Sugar

(Ames Company Elkhart Ind)

Glycosuria (p 3673) may be qualitatively detected and quantitatively approximated through use of a pocket sized kit with test tablets (containing anhydrous copper sulfate anhydrous sodium hydroxide citric acid and sodium bicarbonate) test tube dropper and color scale The reaction also may be used on cerebrospinal fluid (p 3734)

1 Place 5 drops of urine in a test tube

2 Rinse dropper and add 10 drops of water

3 Add 1 test tablet to test tube Observe spontaneous generation of heat with boiling of solution

4 After fifteen seconds match color of fluid in test tube against scale provided with kit In absence of glycosuria fluid remains clear and blue With sugar in urine fluid becomes densely turbid and undergoes color changes from green through dirty brown to copper A flocculent turbidity without color change may be ignored

Galatest Dry Reagent for Detection of Urine Sugar

(Denver Chemical Manufacturing Company New York City)

The Galatest powder (Denco) is a dry reagent compo ed of a bismuth salt sodium hydroxide and sodium silicate In the presence of a reducing sugar a grey or black color is produced by formation of metallic bismuth in a finely divided partially colloidal state The reaction takes place in approximately thirty seconds It is not modified by large amounts of other urinary products either normal or abnormal except for lactose in excess of 2%

1 Shake bottle containing powder before use

2 Deposit mall mound of powder on a piece of plain white paper

3 U ing a dropper deposit one small drop of urine on powder Do not flood powder with urine The test al o may be performed with cerebrospinal fluid (p 3734)

4 In the absence of urinary sugar the white powder takes on color of urine In presence of sugar powder turns grey (0 2%) to black (1% or more) Any color other than grey or black is unimportant in the test as it is most likely due to the presence of malic acid urea compounds or medicine which the patient may have taken

5 To approximate percentage of sugar in particular urine match color of powder against test chart In presence of more than 1% urine may be diluted with equal parts of water and re tested until quantity is more accurately approximated

6 The simplicity of the test recommends it for home u e by patients particularly diabetics under insulin therapy (p 1246)

7 After use vial is tightly capped as hygroscopic powder must be protected from moisture at all times Each vial provides sufficient material for about 200 tests

Acetone Galatest

(Denver Chemical Manufacturing Company New York City)

Acetone test (Denco) is a dry reagent composed of sodium carbonate ammonium sulphate and nitroprusside in anhydrous form In presence of acetone (p 3680) powder turns a shade of purple intensity depending on quantity of acetone Reaction takes place in about sixty seconds and is performed in the manner of the dry test for glycosuria

1 Deposit a small mound of powder on a piece of paper

2 Add 2 or 3 drops of urine to saturate the powder Be sure that entire mass of the powder is completely moistened!

3 In presence of acetone powder turns some shade of purple and may be compared against color chart In absence of acetone powder *takes on a greyish yellow color The simplicity of the test recommends* it particularly for home testing by diabetics (p 1246)

4 The following substances present in urine in pathological conditions *did not give false positive reactions nor did the deep color of* the urine due to their presence prevent the reading of a positive test.

Albumen	Acriflavin
Bile salts	Methylene blue
Blood	Silver nitrate
Creatinine	Crystals
Urobilin	Sulfamids
Urobilinogen	

Hematest

(Ames Company Elkhart Ind)

A dry test for occult blood in urine or stool (p 3728) is performed with reagent tablets containing calcium acetate tartaric acid strontium peroxide and orthotolidin

1 Make a suspension of stool in water Urine is tested as voided
2 Add a drop of specimen to the small square of filter paper that is packaged with tablets
3 Place hematest tablet in center of moist area allow two drops of water to trickle from top of tablet to paper
4 In presence of occult blood *a blue color develops on the filter paper* around hematest tablet within two minutes Disregard discoloration of tablet itself and of filter paper directly under tablet If no blood is present paper will not change color although the tablet may turn a faint blue The test is responsive to dilutions of 1/20 000
5 After opening bottle cotton is not replaced The bottle is stored at room temperature away from direct sunlight and must be tightly stoppered

LAMBLIASIS

[See Giardiasis]

LEISHMANIASIS

[Kala Azar Daukalin Dum Dum Fever Tropical Splenomegaly Ponos Aleppo Boil Oriental Sore]

Principles of Diagnosis and Therapy

1 Systemic leishmaniasis is most effectually treated with pentavalent antimonials (p 534 and Fig 89 p 535)

2 Mucocutaneous or American leishmaniasis and cutaneous or tropical leishmaniasis are best treated with trivalent antimony (Fig 971 p 3317 and Fig 973 p 3319)

3 Each of the manifestations of leishmaniasis is the result of invasion of tissues by Leishmania donovani (Fig 972 p 3318) transmitted from man to man or from an animal reservoir such as the sandfly to man

Practical Management

Immediate Care

1 For treatment of systemic leishmaniasis ethylstibamine (neo ti bosan) is generally regarded as the preparation of choice Ethylstibamine is commercially available in ampuls containing 0 3 gm The ampul is packaged with an ampul of diluent containing 6 cc so that a freshly prepared 5% solution is easily improvised An initial probatory intravenous injection of 0 1 gm is given (2 cc of 5% solution) On alternate days the injection is repeated using 0 2 gm (4 cc of 5% solution) on the third day 0 25 gm (5 cc of 5% solution) on the fifth day and the maximum do e of 0 3 gm (6 cc of 5% solution) on the seventh day If there are no serious reactions the maximum do e is continued until the patient has received a total of 17 injections

2 As an alternative to ethylstibamine stibamine glucoside (neostam) is suggested This preparation is commercially available in vials containing 0 1 0 5 1 and 5 gm doses Neostam is given intravenously in an initial probatory dose of 50 mg By increments of 50 mg the dose is increased to a total maximum dose of 250 mg Of this amount 10 or 11 injections are given for a complete course to total 2 6 to 2 8 gm

3 In the Egyptian Sudan where the di ease is resistant the United States Navy recommends injections of stilbamidine isethionate A freshly prepared solution is made in 10 cc of sterile distilled water which must not be heated The initial dose is 1 mg per kilogram of body weight The maximum dose is 150 mg given every other day for fifteen injections

4 For treatment of American mucocutaneous or tropical cutaneous varieties trivalent antimony is advised Most authorities prefer stibophen

(neostimosan fuadin) marketed in 5 cc ampuls containing 6 3% of the drug On the first day 1 5 cc is injected intramuscularly The second injection on the next day is increased to 3 5 cc Thereafter on the third fifth seventh ninth eleventh thirteenth and fifteenth days 5 cc are deposited to total 40 cc of 6 3% solution The course may be repeated after one or two weeks Thereafter stibophen is given once every seven to fourteen days for several weeks to prevent relapse

5 Successful therapy has also been reported using diramin (p 4224) a preparation commercially available in ampuls containing 2 cc of an aqueous solution (1 cc equals 8 5 mg metallic antimony) The usual dose is 2 cc every second day for five to fifteen intravenous injections though larger doses up to 4 cc are well tolerated

LEPROSY

(Hansen s Disease)

Principles of Diagnosis and Therapy

1 Once the diagnosis of leprosy has been established (p 273 Figs 36–39 pp 274–276) refer the patient to the National Leprosarium at the United States Marine Hospital Carville Louisiana

2 At Carville specific therapy is conducted with promin diasone or promizole

3 With promin an initial intravenous dose of 1 gm is given If patient tolerates this amount dose is increased by daily increments of 0 5 to 1 gm until a total of 5 gm is injected When maximum dose has been achieved injections are given daily for two weeks followed by treatment holidays of one week provided that no serious toxic manifestations develop (p 4552)

4 Diasone (not commercially released as yet) has the advantage over promin in that it can be given orally According to the method used in Hawaii 0 3 gm are ordered in capsule form three days a week If the dose is well tolerated each dose is increased by increments of 0 3 gm until the patient takes maximum amount of 1 2 gm Thereafter the maximum dose of 1 2 gm is given three times weekly Later if course is favorable 0 3 gm are given on alternate days Each dose again is increased by increments of 0 3 gm until patient receives a weekly total of 2 7 gm

In Mexico larger initial doses up to 1 gm daily for seven days are employed Thereafter 1 2 gm are given daily for seven days and 1 6 gm daily thereafter until the condition is relieved or toxic symptoms develop Diasone therapy is interrupted for two weeks every two months

5 Promizole therapy is conducted in the manner of diasone using tablets given orally An initial dose of promizole is 0 5 gm The dose is increased daily by increments of 0 5 gm until the patient takes 6 to 8 gm daily unless toxic symptoms intervene sooner Promizole appears less toxic than diasone

6 While on sulfone therapy constant observation of urine and blood is necessary Injections of liver extract thrice weekly may prevent development of anemia Transfusions are required if hemoglobin falls below 8 gm per 100 cc and erythrocytes below two million On development of agranulocytosis deposits of penicillin are recommended

7 To the list of useless or obsolete preparations (p 277) now may be added streptomycin (214 388) penicillin diphtheria toxoid quinacrine and chaulmoogra oil (p 277)

8 Once regarded as a specific in leprosy chaulmoogra oil has been superseded by sulfones

9 Investigationally sulphetrone has some promise and sterogyl a proprietary is under trial in Brazil (p 4533)

LEUKEMIA ACUTE

[See Blood and Blood forming Organs Neoplasms of]

LEUKEMIA CHRONIC LYMPHATIC

[See Blood and Blood forming Organs Neoplasms of]

LEUKEMIA CHRONIC MYELOID

[See Blood and Blood forming Organs Neoplasms of]

LISTERIA MONOCYTOGENES INFECTIONS

Principles of Diagnosis and Therapy

1 Listeria monocytogenes is a gram positive rod shaped non sporeforming bacillus It occurs in smooth and rough forms

2 In man and sheep Listeria may produce bacteremia and meningo encephalitis *There are no distinctive clinical features The diagnosis* rests wholly on isolation of the organism from blood or cerebrospinal fluid

3 Clinically and experimentally Listeria monocytogenes is susceptible to sulfonamides but insensitive to penicillin

4 Because of the rarity of human Listeria infections and the severity of clinical manifestations massive dose sulfonamide therapy is suggested Use a priming intravenous injection of 2 5 gm each of sodium sulfadiazine and sodium sulfamerazine diluted to at least 200 cc with saline or preferably molar lactate

5 Maintain sulfonamide levels by daily oral doses of 2 to 3 gm each of sulfadiazine and sulfamerazine with 4 gm of sodium b carbonate

6 Concurrently with sulfonamide prescribe daily doses of 200 mg of antihistamine using pyribenzamine or benadryl for possible prevention of hypersensitivity phenomena

LITMOCIDIN

Litmocidin is an antibiotic derived from Proactinomyces cyaneus Litmocidin strongly inhibits growth of staphylococci streptococci tubercle bacilli and V comma Litmocidin under experimental investigation is not commercially available

LL 47

A mold product derived from Aspergillus Under experimental investigation for activity against influenza virus Not commercially available

LOAIASIS

(See Filariasis)

LUPUS ERYTHEMATOSUS, ACUTE DISSEMINATED

General Principles of Diagnosis and Therapy

1 Regard acute disseminated lupus erythematosus (Fig 997 p 3400) as a chronic tuberculin type allergic hypersensitivity (p 4169)

2 Among the striking clinical features (p 3399) are predominant occurrence in females between the ages of 12 and 30 years presence of thermal and photo sensitivities absence of tuberculous lesions suspicion of streptococci as sensitizing bacterial allergens and failure of all forms of specific pharmacotherapy including autohemotherapy blood transfusions and administrations of quinine liver testosterone propionate nicotinamide bismuth gold and sulfonamide

3 Of recommended therapeutic preparations gold and sulfonamides particularly appear dangerous because of their own tendencies to produce hypersensitivity phenomena (p 4179)

4 Prefer to use large doses of antihistamine parenterally and orally For injection deposit 5 cc of 1% benadryl (50 mg) twice or thrice daily if the patient is confined to bed Supplement this with oral doses of at least 800 mg daily of pyribenzamine or benadryl for as long as antihistamines are tolerated

5 Until preparations are commercially available make application for cortisone to Merck and Co Rahway N J or to Dr Chester S Keefer Chairman National Academy Allocation Committee 2101 Constitution Ave Washington D C for ACTH to Dr John R Mote Armour and Co Chicago Illinois Meantime make clinical trial of artisone (Wyeth) and percorten (Ciba) purchaseable in the open market In the use of the latter inject 1 cc intramuscularly (equivalent to 5 mg desoxycorticosterone) followed within five minutes by intra venous introduction of 10 cc of 10% ascorbic acid (1 gm) Unless prompt and dramatic improvement is noted with artisone and per corten—ascorbic acid abandon therapy after three or four consecu tive daily injections

6 Protect the patient from potential allergens including sunlight pollens drugs serums cosmetics and foods to which sensitization occurs frequently (milk and dairy products eggs wheat strawberries etc)

7 Carry out the details for treatment of bacterial allergy (p 4249)

8 Consider supplementation with vitamin D_2 Use oral cap ules of drisdol N N P (calciferol) in doses of 50 000 units thrice daily for several months Watch out for toxic manifestations due to hypercalcemia (anorexia nausea vomiting abdominal pain fatigue thirst polyuria and the development of renal crystalluria or calculosis)

9 With gastric intolerance substitute calciferol parenterally (Kremers Urban) Inject intramuscularly 0 1 to 0 3 cc daily of a solu tion containing 500 000 U S P units of irradiated ergosterol to the cc

LUPUS ERYTHEMATOSUS CHRONIC

Principles of Diagnosis and Therapy

1 Regard chronic lupus erythematosus (Figs 995 and 996 p 3395) as a manifestation of chronic tuberculin type allergic hypersensitivity (p 4169)

2 Conduct therapy as in the acute variety but exercise explicit pre cautions to prevent further exposure to allergens particularly if patient is ambulatory

3 In addition to recommended therapeutic measures for acute lupus syndrome try oral administration of 2 tablets of bismitrate three times daily for a month

4 Protect the patient while ambulatory with sunburn protective to filter out ultraviolet rays (p 3140)

5 In desperation consider reference of the patient to the specialist provided with facilities for injection of nitrogen mustard

LUPUS VULGARIS

Principles of Diagnosis and Therapy

1 In contrast to lupus erythematosus regard lupus vulgaris (p 3262) as a true tuberculosis of the skin (Fig 951B p 3263)

2 Start with systemic therapy using capsules of drisdol N N R (calciferol vitamin D_2) in doses of 50 000 units thrice daily for several months

3 Lesions may show some exacerbation after the first two or three weeks of treatment Later they should soften and flatten

4 Watch out for manifestations of hypercalcemia due to vitamin D_2 These include anorexia nausea vomiting abdominal pain fatigue thirst polyuria and the development of renal crystalluria and concretions Should untoward manifestations develop interrupt vitamin therapy temporarily but resume later

5 Encouraging but not universally successful results of vitamin D_2 therapy have been reported Patients are placed on an unrestricted diet except for limitation of milk to one pint daily and a complete ban on cheese and mineral oil

6 For patients resistant to vitamin treatment alone drisdol may be combined with injections of streptomycin Despite previous use of larger doses the practitioner is warned not to exceed 0 5 to 1 gm daily for forty two days This latter precaution is dictated by efforts to prevent development of neurovestibular toxicity and bacterial fastness (p 4610)

7 In view of the tendency of tuberculosis to produce sensitizing phenomena give antihistamine with vitamin therapy whether or not streptomycin is used in conjunction Daily oral doses of 200 mg of pyribenzamine or benadryl are suggested

8 Very few patients fail to respond to the routine above described Should failures be encountered however they are to be referred to the specialist for consideration of local treatments which include efforts to destroy the lesion without scarification by use of Finsen or Kromeyer lamps electrodesiccation electrocoagulation application of 5 to 10% pyrogallic acid (p 3125) roentgen irradiation or freezing with carbon dioxide snow (p 3785)

9 In view of the equivocal results of gold as a bactericide in tuberculosis of its toxicity and tendency to produce hypersensitivity reactions chrysotherapy is definitely not recommended despite many enthusiastic reports to the contrary

LYMPHOCYTIC CHORIOMENINGITIS

General Principles of Diagnosis and Therapy

1 Lymphocytic choriomeningitis is another non suppurative encephalomyelomeningitis (p 442) of virus origin

2 The infection is capable also of producing manifestations resembling grippe and pneumonitis (p 449)

3 *Among lower animals the virus has been isolated from mice* which may be the human vectors

4 The diagnosis is established in convalescence by demonstration of complement fixing and virus neutralizing bodies

5 There is no specific prophylactic or curative therapy available at present On the basis of encouraging results in virus pneumonitis ornithosis and lymphogranuloma venereum administration of aureomycin or chloramphenicol merits trial

6 Since the virus has been isolated from patient s urine the latter should be sterilized before disposal into the sewage system Traps should be set for mice

LYMPHOPATHIA VENEREUM

[Lymphogranuloma Venereum Climatic Bubo Tropical Bubo Esthiomene Poradenitis Nicolas Favre s Disease]

General Principles of Diagnosis and Therapy

1 Lymphopathia venereum is not as is generally thought a localized infection of genitals rectum and sigmoid It is a systemic invasion with an organi m closely allied to that which produces ornithosis psittacosis and virus pneumonitis

2 In all likelihood the microbe of lymphopathia venereum is mid way between rickettsias and viruses

3 The diagnosis of lymphopathia venereum rests on the clinical appearance of the lesion (Fig 72 p 470) and the Frei test (Fig 72D p 470)

4 The Frei test is performed intradermally with Frei antigen (Lederle) or Lygranum S T (Squibb) Inject 0 05 to 0 1 cc intracutaneously into the skin of the flexor surface of the right forearm Introduce a like amount of control in the left forearm Observe reactions at 48 and 72 hours

5 The patient with lymphopathia venereum must be suspected of having acquired other venereal infections at the same time Particularly follow up observations include serologic tests for syphilis Additionally *during the first examination examine the chest for evidences* of atypical pneumonitis

6 The etiologic agent of lymphopathia venereum is sensitive to sulfonamide streptomycin aureomycin and chloramphenicol Sulfonamide is least expensive but aureomycin and chloramphenicol are most potent and least hazardous

7 If sulfonamides are used in treatment give sulfadiazine in a daily dose of 2 to 4 gm for ten to fourteen days After a rest period of a week repeat treatment if necessary

7 Streptomycin therapy requires intramuscular injections of 0 5 gm of dihydrochloride four times daily for fourteen days This treatment is impractical particularly for ambulatory patients

8 The most efficient and safest method of therapy utilizes aureomycin or chloramphenicol *preferably the former if the patient tolerates* the antibiotic well Give a priming dose of 50 mg per kilogram of body weight (3 5 gm for average adult weighing 150 lbs) To avoid gastric irritation 2 capsules each of 250 mg are swallowed every ten or fifteen minutes accompanied by a small amount of milk cream cheese ice cream or fruit juice After four hours start maintenance doses using the same amount as for the priming dose but divided in *4 equal parts given at six hour intervals If aureomycin is not tolerated* substitute chloramphenicol

9 After the venereal lesion has healed perform proctoscopic examination to ascertain whether rectal damage has been done The latter may later result in the formation of strictures requiring dilatation or surgical repair

10 Obsolete are antimony gold and hormonal treatments

MADUROMYCOSIS

(Mycetoma)

Principles of Diagnosis and Therapy

1 Treat maduromycosis (Fig 969 p 3314) as actinomycosis (p 4141)

2 Encouraging results have been obtained with the use of large doses of iodides

3 Excision drainage and even amputation may have to be considered *in management of local lesions*

MALARIA

(Paludism Ague Blackwater Fever Jungle Fever)

Principles of Diagnosis and Therapy

From the time of its introduction as a decoction of cinchona bark until the exigencies of war compelled belligerents to devise synthetic substitutes the specificity of quinine in malaria was regarded as a medical axiom although millions of human beings continued to suffer recurrences of the disease despite large and continued doses of the alkaloid (p 507)

Writing in the 14th edition of the Encyclopedia Britannica (1940) Sir Ronald Ross Consultant in Malaria for the British Ministry of Pensions and the War Office gave many intimations of the inadequacies of quinine as a chemoprophylactic in paludism

Quinine prophylaxis has been of value on particular occasions such as in tiding a body of troops over a critical period of fighting or passing through a heavily infected area in that it has checked attacks of malaria during that time Bodies of troops in Salonika who were given quinine daily remained free as long as they were taking it but went down with malaria as soon as they stopped it showing that they were infected in spite of it

Measures to rid carriers of the parasite are most difficult to put into practice There is no settled or fixed dosage or time of administration of the specific remedy quinine or other of the cinchona bark extracts

As to active anti malarial treatment Sir Ronald Ross stated The fact that moderate doses of quinine will control actual attacks within a few days was fully verified (following the outbreak of malaria at Salonika in 1916) with very few exceptions Almost every form of treatment that had ever been suggested—enormous doses of quinine reaching 100 grains per diem smaller doses continued for three weeks or more additional medication with arsenic and other drugs continuous doses lasting for a month and various kinds of interrupted dosage—all proved uncertain Thirty grains of quinine continued every day for three weeks proved a failure Intramuscular injections and even intravenous injections did no better Men who were presumed to be cured relapsed again after returning to duty a large proportion of those infected with malaria became almost useless for further service Numerous nostrums advocated for malaria proved valueless the only exceptions being one or two arsenical preparations which however were no better than ordinary quinine

Despite these modifying statements concerning its specificity in malaria Sir Ronald did not question the preeminence of quinine as an antimalarial except to intimate that the important factor of building up and maintaining the general health so as to assist the natural forces of the body to eliminate the malarial parasite must not be forgotten

With advent of World War II the problem of malaria became more urgent particularly to American troops deployed in South Pacific areas Africa the Middle East China Burma and India

Malaria soon became the outstanding medical problem of the war not from the standpoint of mortality because there were relatively few deaths but because of the high degree of morbidity Although the assertion is repeatedly made that malaria is a disease for which there are specific therapeutic drugs and that it is a simple matter to overcome the infection the fact remains that malaria is a most difficult disease to eradicate completely For certain types of malaria particularly Southwest Pacific vivax malaria it seems that complete recovery is entirely dependent upon the individual s defense mechanism This is evidenced by the frequent relapses which occur after therapeutic measures considered adequate in patients who have had no opportunity to become re infected (Coggeshall in Cecil s Textbook of Medicine 7th edition p 433)

The problems of the Allied Medical Command relative to malaria intensified when Japan cut off supplies of quinine through acquisition of the Dutch colonial empire Preparation of effective synthetic antimalarials then became a military matter of as much urgency as supplies of food and ammunition As a result innumerable synthetics were produced and tested for antimalarial activity From these studies there evolved many potent preparations At first quinacrine (atabrine) and pamaquine (plasmoquin) exhibited their superiority over quinine despite their toxicity By the end of World War II new synthetics replaced previously haled miracle drugs For security reasons these products bore code numbers SN 7618 SN 12837 SN 13272 SN 13274 SN 13276 etc and none was available for use by the practitioner With astounding speed and efficiency the Council on Pharmacy of the American Medical Association clarified the antimalarial situation and gave official sanction to chlorguanide known also as paludrine SN 12837 and guanatol hydrochloride to chloroquine alias aralen SN 7618 nivaquine, and resochin to pentaquine (SN 13276) and to isopentaquine (SN 13274) To establish indications for use of new antimalarial and evaluate their efficiency in comparison to quinine it is necessary to review the life cycle of the malarial parasite (p 507) identify on blood spreads plasmodium vivax plasmodium falciparum and plasmodium malariae (Fig 85 p 512) and differentiate the two commoner forms of plasmodia as set forth in Table (p 4394)

DIFFERENTIAL DIAGNOSIS OF VIVAX AND FALCIPARUM MALARIAE FROM THICK AND THIN BLOOD SPREADS

Observation	Vivax (Fig 38 p 508)	Falciparum (Fig 84 p 511)
Parasitized erythrocyte	Larger and paler than normal	Normal or smaller than normal
Schuffner s granules	Present	Absent
Maurer s dots	Absent	Present
Pigmentation	Eosinophilic stippling	Brassy color but no pigmented spots
Parasites	In various stages	Only rings and crescents *except terminally*
Ring Forms	Approximate the diameter of the red cell	Smaller than the red cell
Ring forms (Marginal types)	Infrequent	Frequent
Multiple infections of cells	Rare	Common
Approximate numbers of parasites	*10 000 per cu mm*	*500 000 per cu mm.*
Cytoplasm of ring	Coarse	Hairlike
Trophozoite	Sprawling	Delicate
Schizonts	Present in peripheral blood *with 12 to 24 merozoites* in grape like clusters	Not seen in peripheral *blood Obtain by marrow* aspiration or spleen puncture Note 18 to 36 very small merozoites in irregular clusters
Gametocytes	*Spherical or oval*	*Typical crescents*

Terminology

A principal difficulty in understanding malaria is its complicated *terminology For purposes of clarification the following glossary* is appended

Active treatment *Symptomatic relief of acute attack without* necessarily effecting radical cure (q v) As an agent in active therapy *quinine is most effective*

Aestivo autumnal malaria Synonym for infection by Plasmodium falciparum

Ague Synonym for malaria

Benign tertian malaria Infection with Plasmodium vivax

Blackwater fever A complicating hemoglobinuria probably due to quinine idiosyncrasy in the malarial patient

Causal Prophylaxis This involves destruction of pre erythrocytic forms probably resident in the liver (Shortt) With effective causal prophylaxis patients remain symptom free after antimalarial is discontinued and do not transmit infection to the biting mosquito Causal prophylaxis is accomplished only by chlorguanide in falciparum invasions Neither chloroquine nor quinine is a true causal prophylactic

Exo erythrocytic phase (pre erythrocytic phase) The exo erythrocytic phase of malarial infection begins when sporozoites are introduced into the host *It terminates when ring forms appear in red cells* Roughly this corresponds to the incubation period of the disease during which Shortt has shown *that sporozoites nest in the liver In this location* only the falciparum form is vulnerable to antimalarials and then only to chlorguanide *a true causal prophylactic*

Cerebral malaria Synonym for severe infections with Pla modium falciparum

Falciparum malaria Infection with Pla modium falciparum Peferred to also as malignant tertian malaria aestivo autumnal malaria and subtertian malaria

Gametogony The sexual phase of development of the malarial plasmodium Microgametocyte and macrogametocyte are derived from schizonts After transference to the digestive tract of the mosquito male and female sexual elements unite to form gametes oocysts and sporozoites later to be introduced into man through bite of mo quito vector

Jungle fever Synonym for malaria

Macro gametocyte The female sexual form of the malarial plas modium is produced by schizonts and demonstrable in peripheral blood (Fig 83 for vivax illustration 24 Fig 84 for falciparum illustrations 26 27 and 28 Fig 85 for malariae illustration 24)

Malignant tertian malaria Synonym for Plasmodium falciparum infections

Maurer s dots Irregular spots seen in parasitized erythrocytes con taining P falciparum (Fig 84 illustrations 9 to 12) Maurer s dots differ from Schüffner s granules and erve to differentiate vivax and falci parum infections

Merozoites A form of the malarial parasite derived from splitting of the mature schizont Merozoites are not demonstrable in peripheral blood They are exo erythrocytic until they attack an erythrocyte and become recognizable as ring forms within the red cell

Micro gametocyte The male sexual form of malarial parasite derived from the schizont Demonstrable in peripheral blood (Fig 83 for vivax illustration 23 Fig 84 for falciparum illustrations 25 26 and 27 Fig 85 for malariae illustration 23) After transferral to the diges tive tract of the mosquito micro gametocytes and macro gametocytes form oocytes and sporozoites later to be introduced into man by bite of mosquito vector

Paludism Synonym for malaria

Plasmodium falciparum See Fig 84 p 511

Plasmodium malariae See Fig 85 p 512

Plasmodium vivax See Fig 83 p 508

Pre erythrocytic phase See exo erythrocytic phase

Quartan malaria Produced by Plasmodium malariae and charac terized by chilling on the fourth day

Radical Cure Relief of symptoms of acute attack freedom from manifestations after drug has been discontinued non transmission of the disease to the mosquito when the patient is bitten during or after administration of the drug unless reinfected Radical cure is accom plished by chloroquine in falciparum by the combination of isopenta quine and quinine in relapsing vivax and by chlorguanide in most vivax infections Quinine alone does not produce radical cure

Ring forms The earliest endo erythrocytic manifestation of the malarial invasion

Schizont A late phase of the endo reticulocytic portion of the life cycle of the malarial parasite The schizont evolves from the trophozoite and terminates its existence on discharge of merozoites in the process of schizogony Schizonts also produce male microgametocytes and female macrogametocytes for the sexual phase of the malarial life cycle (Fig 83 for vivax illustrations 16 to 20 Fig 84 for falciparum illustrations 16 to 20 Fig 85 for malariae illustrations 15 to 20)

Schuffner s granules Schuffner s granules are coarse red dots seen in parasitized erythrocytes in the vivax form of malaria (Fig 83 illustration 5) Schuffner s granules help to differentiate vivax from falciparum

Sporozoite The toothpick shaped form of the malarial parasite as it is liberated from the oocyte in the stomach of the mosquito vector Sporozoites make their way to the salivary glands of the mosquito from which they are transferred to man in the act of biting Sporozoites are not identified in peripheral blood

Subtertian malaria Synonym for Plasmodium falciparum

Suppression Suppression is the therapeutic principle by which the patient though relieved of acute symptoms remains infectious to the mosquito vector and suffers relapse after discontinuance of the drug In all probability the suppressive antimalarial drug attacks only endo erythrocytic forms the parasite retreats to the parenchymal cells of the liver where it remains inaccessible to therapy (Shortt) and relapses are encountered Compare chloroquine suppression in vivax to radical care by chlorguanide in falciparum

Tertian malaria A term used for both vivax (benign) and falciparum (malignant) infections The term merely implies that the chill occurs on the third day

Trophozoites The endo erythrocytic non reproductive phase When ring forms develop pseudopodia the trophozoitic phase begins It continues through formation of the schizont (Fig 83 for vivax illustrations 1 to 20 Fig 84 for falciparum illustrations 1 to 20 Fig 85 for malariae illustrations 1 to 20)

Antimalarial Agents

Tremendous forward strides have been taken in the eradication causal prophylaxis suppression and radical cure of malaria Complete conquest of the disease is a goal that does not appear too far distant

The current roster of antimalarials with their principal therapeutic uses and potential toxicity is shown in the table (p 4397)

Practical Management

Prophylaxis

1 For causal prophylaxis of falciparum prescribe 100 mg of chlorguanide hydrochloride (Abbott) or guanatol hydrochloride (Lilly) three times daily twice a week Start two weeks before entering malarial zone Continue four weeks after departure

2 For suppression of vivax order 250 mg of chloroquine diphosphate (aralen Winthrop) twice daily twice a week Start two weeks before entering malarial zone Continue four weeks after departure

ANTIMALARIALS

Product	Therapeutics	Toxicity
Aralen (Winthrop)	See chloroquine	
Atabrine	See quinacrine	
Camoquin	Newly developed synthetic with decided effect on vivax gametocytes asexual forms of vivax and falciparum See text	Negligible
Chlorguanide (paludrine guanatol hydrochloride SN 12837) N N R	With chloroquine best all purpose antimalarial Prefer for causal prophylaxis suppression and cure of falciparum See text	Negligible
Chloroquine (aralen sontochin resochin SN 7618) N N R	With chlorguanide best all purpose antimalarial Use for suppression and treatment of vivax and quartan infections Second choice to chlorguanide in falciparum For relapsing vivax switch to pentaquine-quinine in combination See also text	Negligible
Euquinine	As quinine	Reputedly less toxic than quinine
Guanatol	See chloroquine	
Isopentaquin (SN 13274) N N R	When commercially available use with quinine for treatment of relapsing vivax in infections See text	Negligible
Melarsen oxide	Antimalarial arsenical used experimentally	Arsenic poisoning (p 122)
Mepacrine	See quinacrine	
Paludrine	See chlorguanide	
Pamaquine naphthoate (plasmoquin) N N R	Replace by less toxic pentaquine quinine combination for treatment of relapsing vivax See text	Considerable (p 519)
Pentaquine (SN 13276)	For use with quinine in relapsing vivax See text	Minor (p 521)
Plasmochin	See pamaquine	
Primaquine (SN 13272)	In experimental use to compete with pentaquine and isopentaquine	Negligible
Quinacrine (atabrin mepacrine) U S P	Replace by less toxic chloroquine for suppression and treatment of vivax See text	Considerable with skin pigmentation (p 520)
Quinine Bisulfate U S P	Most rapid antipyretic effect in acute attack but not a causal prophylactic Use with pentaquine in relapsing vivax infections See text	Considerable (p 518)
Pesochin	See chloroquine	
SN 7618	See chloroquine	
SN 12837	See chlorguanide	
SN 13272	See primaquin	
SN 13274	See isopentaquin	
SN 13276	See pentaquine	
Sontochin	See chloroquine	
Totaquine	Use as quinine An impure preparation that has the advantage of lesser cost	As quinine (p 518)

3 For combined causal prophylaxis and suppression of all types of malaria prescribe chlorguanide or guanatol on Monday and Thursday and aralen on Tuesday and Friday

Immediate Care

1 Obtain thick and thin spreads of peripheral blood from fingertip Stain by Wright method Attempt to identify parasite and differentiate between vivax and falciparum If in doubt assume that the vivax form is present if the patient is an American who has not been out of the country for considerable time or if there is a history of previous attacks

2 Assuming that the infection is by vivax prefer chloroquine diphosphate (Aralen Winthrop) Prescribe 4 tablets each of 250 mg to total 1 gm At the end of 6 24 and 48 hours order 2 tablets each of 250 mg until a total of 10 tablets or 2 5 gm has been administered over the course of the forty eight hours

3 If it is assumed or proven that the infection is falciparum prefer chlorguanide hydrochloride (Abbott) or guanatol hydrochloride (Lilly) Order 100 mg 3 times daily for ten days

Continuing Care (Favorable Course)

1 For suppression of vivax infection prescribe 2 tablets of chloroquine diphosphate (aralen Winthrop) each of 250 mg twice weekly i e on Mondays and Thursdays

2 For causal prophylaxis and suppression of falciparum infections order 100 mg of chlorguanide hydrochloride (Abbott) or of guanatol hydrochloride (Lilly) 3 times daily twice weekly i e on Mondays and Thursdays

Continuing Care (Unfavorable Course)

1 If patient gives history of frequent recurrences assume that present attack is a relapse most likely of vivax origin Prescribe 1 tablet of 10 mg of pentaquine phosphate (Abbott) and 0 5 gm of quinine sulfate 3 times daily for fourteen days

2 If patient is severely ill comatose or unable to swallow resort to parenteral introduction of antimalarial Improvise a solution of 0 2 gm of chloroquine base (aralen) in 5 cc of sterile aqueous solution and deposit intramuscularly For second choice obtain ampul of atabrine (Winthrop) containing 200 mg with another ampul of 10 cc of sterile distilled water Inject 10 cc in each buttock to total 20 cc containing 400 mg of antimalarial For third choice prepare a solution of quinine dihydrochloride Dissolve 0 6 gm in 300 cc of sterile physiologic saline Introduce intravenously by the slow drip method

3 For investigational use only are camoquin isopentaquine melarsen and primaquine

4 As quinine substitutes use euquinine or totaquine (p 4397)

5 Obsolete because of toxicity are pamaquine (plasmodium) and quinacrine (atabrine) for oral use

MALE REPRODUCTIVE SYSTEM NEOPLASMS OF

Acce_sibility of the structures of the male reproductive system affords the practitioner an unusual opportunity for early diagnosis of asymp tomatic malignancy The seasoned practitioner never omits palpation of scrotal contents and prostate during routine physical examination Additionally he feels the male brea t particularly in those patients who have been given androgen therapeutically (p 4192)

NEOPLASMS OF THE MALE EXTERNAL GENITALS

Practical Management

1 During routine examination palpate scrotum Make note of any unusual swelling or tumor (p 2441)

2 In the dark room transilluminate scrotum and determine whether swelling is translucent or opaque

3 With translucent swelling su pect hydrocele Prepare to aspirate fluid and submit to clinical pathologist for cytodiagnosis by Papani colaou method

4 Obtain blood for serodiagnosis of syphilis and malignancy (p 4431)

5 Get chest x rays for evidences of tuberculosis

6 With opaque swellings consider reference to urologist or surgeon

7 In the absence of evidences of infection insist on biopsy of opaque tumor or actual exploratory examination

NEOPLASMS OF PROSTATE AND MALE BREAST

1 During the course of each routine examination palpate the pro state With positive findings refer the patient to the consultant surgeon and request a needle biopsy

2 Obtain blood for serodiagnosis of syphilis and malignancy (p 4431) and for acid phosphatase determination (p 728)

3 Order cystoscopic examination to observe intravesical appearance of prostatic tumor

4 On suspicion of malignancy prepare patient for prostatectomy and castration

5 Po toperatively administer estrogen (p 4325)

6 During estrogen therapy constantly re-examine the male breast for evidences of gynecomastia and of possible malignancy On sus picion in ist on total mastectomy

MANDELIC ACID N F

A non metabolizable substance used as a urinary antiseptic Admin istered orally mandelic acid is excreted in the urine When *pH* is 5 5 or le s urine becomes bactericidal or bacteriostatic for E coli Aerobacter aerogenes Streptococcus fecalis Proteus Pseudomonas Alkaligenes Salmonellae and Shigellae For optimum effect reduce fluid intake to 1000 cc so that a concentrated urine is voided

Available Products

Ammonium Mandelate (Squibb) Enteric coated tablets 0 3 and 0 5 gm
Camdelate (Abbott) Tablets 0 543 gm of calcium mandelate
Mandelic Acid (Mallinckrodt Merck) Powder 4 gm thrice daily
Elixir of Mandelic Acid (Lilly) Twelve cc = 4 gm
Syrup Ammonium Mandelate (Smith) Fifteen cc = 4 gm
Mandelic Acid (0 3 gm) with *Ammonium Chloride* (0 23 gm) Enseals (Lilly)

Therapeutics (p 4626)

As a urinary antiseptic give 3 gm four times daily or the equivalent Use test papers to assure pH of 5 5 or less in the urine Supplement with ammonium chloride if necessary Continue mandelic acid or one of its derivatives *for twelve to fourteen days unless the patient develops* nausea diarrhea dysuria or hematuria

Mandelic acid is contraindicated in patients with renal insufficiency

MEASLES

(Roseola Morbilli)

General Principles of Diagnosis and Treatment

1 The virus of measles (Fig 64 p 410 Fig 65 p 411) is *resistant* to antibiotic agents with the possible exception of aureomycin and chloramphenicol

2 Measles vaccine under experimental observation has *not had* large scale human trial and is not commercially available

Practical Management

Prophylaxis

1 Human gamma globulin preferably given on the fifth day after *exposure completely protects in 79 per cent* of instances and modifies the disease *in the remaining 21 per cent* For children under five years of age intramuscular injections of 1 to 2 5 cc are required older children and adults need 5 to 15 cc according to the undernoted schedule (p *4401)*

2 Modified measles produces permanent immunity and is preferred to complete prevention

Immediate Care

1 Institute general measures for nonspecific treatment of the infected patient (p 67)

2 Patients with clinical measles require penicillin injections for

prevention and treatment of pyogenic complications Give oral doses of crystalline penicillin G or aluminum penicillin in food or drinks using 50 000 units every 3 or 4 hours or deposit procaine penicillin G in aqueous solution or suspension in a dose of 300 000 to 600 000 units once daily

TABLE OF DOSAGES OF IMMUNE SERUM GLOBULIN (HUMAN)

Patient's Weight—lbs.	Dose for Modification (0 02 cc per pound)	Dose for Prevention (0 1 cc per pound)
15	0.30 cc	1.50 cc.
20	0 40 cc	2.00 cc.
25	0.50 cc	2.50 cc.
30	0 60 cc	3 00 cc.
35	0 70 cc	3.50 cc.
40	0.80 cc.	4 00 cc.
45	0 90 cc	4 50 cc
50	1 00 cc	5 00 cc
60	1.20 cc	6 00 cc
70	1 40 cc	7 00 cc
80	1 60 cc	8 00 cc.
90	1.80 cc	9 00 cc
100	2.00 cc.	10 00 cc
125	2.50 cc.	12.50 cc.
150	3 00 cc	15 00 cc

3 Prescribe oral antihistamine (200 mg daily of pyribenzamine or benadryl) to prevent hypersensitivity reactions especially measles encephalopathy (p 4307)

4 Aureomycin may prove even more useful than penicillin since it is virucidal as well as active against secondary invaders

5 Human Measles Immune Serum is obsolete

MELITURIAS

The term melituria is used to denote the presence in urine of abnormal amounts of sugar In its broadest sense melituria is an inclusive concept that covers glycosuria levulosuria pentosuria lactosuria galactosuria fructosuria maltosuria and sucrosuria

Of meliturias only hyperglycemic glycosuria of diabetes mellitus (p 1264) has important clinical significance for patient and practitioner Hence reduction of Benedict solution (pp 3676 and 3677) challenges the physician to differentiate clearly between an innocent melituria and the significant hyperglycemic glycosuria of the diabetic

For clarification of melituria the following protocol is suggested

1 In the presence of physician or nurse have patient void into a clean vessel to preclude accidental or deliberate contamination of the specimen

2 Exclude pseudo-reduction of Benedict solution due to substances other than sugar (p 3674)

3 Identify sugar responsible for melituria according to accompanying chart (p 4402) Additionally test for acetonuria (p 4384)

4 To confirm tests performed in office laboratory send a 24 hour sample to clinical pathologist for additional information including polariscopy and crystallization with phenylhydrazine

5 Observe effect on melituria of hyperalimentation using a diet high in concentrated carbohydrate foods (p 672)

6 Observe effect on melituria of insulin injection (p 1241)

7 Obtain bloods for sugar determinations (p 3714) after patient has fasted twelve hours and again one and two hours after ingestion of dextrose test meal (p 3716)

8 If blood sugars are within range of normal consult Table of Differential Diagnosis of Non Hyperglycemic Glycosurias (p 4405)

9 In presence of elevated blood sugars consult Table of Differential Diagnosis of Hyperglycemic Glycosurias (p 4407)

10 Bear in mind that diabetes mellitus is a disturbance of such great frequency that it may co exist in potential or full blown form with any other melituria

Differential Diagnosis of

Meliturias

In the investigation of melituria the practitioner recalls these important axioms (1) The presence of melituria does not necessarily signify that the patient suffers from diabetes mellitus (2) Absence of melituria does not necessarily exclude the diagnosis of diabetes mellitus since the patient may have been aglycosuric at the time of voiding

Observation	Glucose	Levulose	Pentose	Fructose	Lactose	Galactose	Maltose or Sucrose
Yeast Fermentation	Yes	Yes	No	Yes	15%	Yes	No
Hyperglycemia	Present	0	0	0	0	0	0
Acetonuria	May be present	0	0	0	0	0	0
Clinical Symptoms of Diabetes Mellitus	May be present	0	0	0	0	0	0
Response to Hyperalimentation	Increase	0	0	0	0	0	0
Response to Insulin	Decrease	0	0	0	0	0	0
Special Tests	Rubner	Borchardt	Bial	—	Rubner	—	—
Polarization	Right	Left	0	0	Right	0	0

See p 4403 Refer to Clinical Pathologist

Borchardt Test

The Borchardt test detects and identifies levulose in urine (see below)

1 Make a 25% solution of hydrochloric acid by adding 2 parts of concentrated hydrochloric acid to 1 part of water
2 To 5 cc of urine add 5 cc of 25% hydrochloric acid, and a few crystals of resorcinol
3 Boil mixture for 30 seconds In presence of levulose solution turns red
4 Cool solution and add solid sodium hydroxide
5 To alkaline mixture add 2 cc of acetic-ether and shake In presence of levulose ether takes on a yellow color

Rubner Test

The Rubner test differentiates lactosuria (p 4404) from glycosuria

1 To 10 cc of urine add 2 gm of lead acetate
2 Shake and filter
3 Boil filtrate Add 2 cc of strong ammonia water
4 Heat mixture In presence of lactose solution turns a brick red and a red preci pitate settles out In presence of glucose solution turns red and a yellow pre cipitate settles out

Bial Test

The Bial test detects pentosuria (see below)

1 Remove glucose from urine by fermentation.
2 Dissolve 1 5 gm. orcinol in 500 cc of 30% hydrochloric acid Add 1 cc of 10% ferric chloride
3 Place 5 cc of reagent in test tube and heat.
4 Remove test tube from flame Add 2 cc of urine drop by drop In presence of pentose a green color develops

Levulosuria

The presence of levulose in urine is detected by reduction of copper salt in Benedict solution (p 3676) and by further differentiation through the Borchardt reaction (above) Verification of the simple test is required and a complete 24 hour yield of urine should be sent to the clinical pathologist for identification of the characteristic osazone crys tals and for polarization since levulose alone of the sugars rotates polarized light to the left

Essential Levulosuria In rare instances levulosuria occurs with glycosuria in severe diabetes mellitus With this exception levulosuria is noted only as a rare metabolic anomaly The condition is familial and benign It is not accompanied by hyperglycemia and is unin fluenced by hyperalimentation or injections of insulin

Essential levulosuria requires no treatment The patient should be informed of the presence of a reducing substance in the urine in order to avoid future error

Pentosuria

Pentosuria is recognized by reduction of copper salt in Benedict solution and by the positive Bial reaction (above) The diagnosis should be verified by the clinical pathologist who may identify the charac teristic pentosazon crystals and obtain specific fermentations with bacteria and yeasts

Alimentary Pentosuria Alimentary pentosuria is a temporary con dition that occurs in normals after ingestion of large quantities of

fruits of high pentose content These include prunes cherries grapes and plums

Alimentary pentosuria has no clinical significance It disappears with the elimination from the diet of high pentose fruit The condition requires no treatment other than notification of the patient of the presence of a reducing substance in urine While there is no evidence that pentosurias produce any later difficulty it may be wise to suggest limited ingestion of high pentose fruits

Essential Pentosuria Essential or chronic pentosuria like essential levulosuria is a relatively rare and benign familial and congenital metabolic anomaly It has no particular clinical significance unless it is mistaken for diabetes mellitus The utilization of other carbohydrates is unimpaired

The patient may follow a normal diet though it may be wise to limit the quantity of high pentose fruits such as prunes cherries grapes and plums

Fructosuria

Fructosuria is an exceedingly rare familial and congenital benign metabolic disorder Fructose causes a reduction of the copper solution in the Benedict test (p 3676) Its final identification requires the assistance of the clinical pathologist since the sugar gives none of the simple reactions that can be performed in the office laboratory (p 4403)

Essential fructosuria requires no treatment except notification of the patient of the presence of the melituria

Lactosuria

Lactose occasionally but not invariably produces reduction of copper salt in Benedict solution (p 3674) It may be identified in the office laboratory through the presence of a red precipitate in the Rubner test (p 4403) More exact identification is possible through assistance of the clinical pathologist who may produce characteristic lactosazone crystals with phenylhydrazine and perform fermentation tests with specific bacteria

Contrary to the general belief lactosuria does not occur normally during pregnancy It is physiologic in the postpartum period and during the puerperium (p 2715) while the mother is lactating

Physiologic lactosuria has no pathological significance Its main importance lies in its recognition lest the physician erroneously conclude that his patient has developed a true diabetes mellitus during the course of child bearing

Galactosuria Maltosuria and Sucrosuria

Galactosuria maltosuria and sucrosuria do not occur spontaneously in health or disease Galactosuria is artificially produced when large quantities of the sugar are ingested for the purpose of testing liver function (p 1949) Maltosuria and sucrosuria result from accidental or deliberate contamination of the specimen when after voiding malt sugar or cane sugar is introduced

Glycosuria (Glucosuria)

Of the meliturias (p 4402) glycosuria alone may have important clinical significance for the practitioner In its presence the compleat practitioner sets himself the task of positively affirming or surely excluding the presence of diabetes mellitus (p 1246)

Pathologic Physiology A minute quantity of sugar undetectable by routine laboratory methods is present in urine at all times A detectable amount may be passed by the normal individual (a) under physiologic conditions (hyperalimentation) (b) during stress and (c) as the result of drug administration (morphine anesthetics etc)

There are at least four mechanisms by which glycosuria may be produced

1 Concentration of glucose in the arterial blood of the glomeruli beyond threshold value (150 to 180 mg $\times$ 100 cc)

2 Excessive rate of glomerular filtration such as occurs in advanced nephropathies (p 2364)

3 Decreased rate of tubular reabsorption as seen clinically in renal diabetes (p 4406) and experimentally in phloridzin poisoning

4 Experimental puncture of the pecific sugar regulating center of the medulla (Claude Bernard)

Of the factors involved in glycosuria only hyperglycemia can be measured by the clinician Even this figure is subject to interpretation since the determination is made on blood obtained from a peripheral vein where the concentration of sugar is lower than in the renal artery Despite this error which has more academic than practical significance glycosurias are divisible into those which occur with a normal blood sugar level (hypoglycemic glycosurias) and those in which there is elevation of fasting sugar or sustained high levels following the test meal (hyperglycemic glycosuria)

Differential Diagnosis of

Non Hyperglycemic Glycosurias

Non hyperglycemic glycosuria may be transitory (alimentary psychogenic pharmacologic or parturient) or more persistent (nephropathic or renal diabetes) Phloridzin diabetes occurs only in the experimental animal

CLINICAL MANIFESTATIONS AND DIAGNOSTIC FEATURES

Alimentary	History of gorging Normal fasting blood sugar and sugar tolerance test (p 1250) Aglycosuria on normal diet May be potential diabetic (p 1246)
Psychogenic	History of emotional or traumatic disturbance Normal tests after quiescence
Pharmacologic	After anesthesia morphine (p 3854) and adrenergens (p 3876)
Pregnancy	In latter months (p 2673) Probably from hyperpituitarism. Unaccompanied by symptoms of diabetes mellitus unless hyperglycemic Non hyperglycemic glycosuria disappears after childbirth Exclude lactosuria postpartum and in puerperium (p 2715)

Nephropathic	With advanced nephropathy (p 2362) especially if due to failure of tubular reabsorption. Note marked depression of renal functional tests but neither clinical symptoms or signs of diabetes mellitus Note that the two conditions may coexist
Phloridzin Poisoning	Experimental lesion of animals Poison prevents tubular reabsorption of sugar as in renal diabetes (p 4406)
Renal Diabetes	Benign metabolic disorder (p 4406) Normal fasting blood sugar and sugar tolerance test (p 1250) Uninfluenced by insulin or hyperalimentation Asymptomatic Requires no treatment

RENAL DIABETES

[Renal Glycosuria Benign Glycosuria Diabetes Innocens]

Renal diabetes is an inborn error of metabolism that has no untoward clinical implication Its primary importance rests in recognition of its benign nature so that the patient is not subjected to treatment for diabetes mellitus (p 1252)

Clinical Manifestations In renal diabetes considerable quantities of glucose appear in the urine at all times The glycosuria is independent of hyperalimentation or fasting it is not eliminated by administration of insulin

In all likelihood the metabolic error is a failure of normal reabsorption of glucose by the renal tubules presumably because of inadequate phosphorylation (Fanconi s syndrome) Patients with renal diabetes resemble animals poisoned with phloridzin they do not have hyperglycemia and the degree of glycosuria is independent of carbohydrate intake

The incidence of renal diabetes is variously estimated Some authorities regard the condition as infrequent whereas others place the incidence as high as 1 to 2 per cent of otherwise normal individuals During World War I the author encountered a large group in a hospital specializing in metabolic abnormalities but has met with only one example in thirty years of private practice

Diagnosis The diagnosis of renal diabetes is established by the constant finding of urinary sugar in individuals who present no symptoms of diabetes mellitus (p 1246) In such patients the fasting blood sugar is within normal limits and the sugar tolerance curve appears normal in all respects ketosis is not encountered when the patient fasts glycosuria does not increase when the patient over eats nor does it tend to lessen when he fasts doses of insulin have little or no effect on the extent of glycosuria the urinary sugar may be identified as glucose (p 3674) thus eliminating the presence of one of the rarer varieties of melituria (p 4402)

Course and Prognosis Authorities differ as to the outlook for patients with renal glycosuria Writing in Cecil s Textbook of Medicine Loeb states that the patient should be considered a potential diabetic and re examined at frequent intervals particularly when a family history of diabetes has been elicited On the other hand Cantarow concludes that so far as can be determined it (renal glycosuria) never results in diabetes mellitus nor in any metabolic derangement whatsoever

In view of the discrepancy between these authoritative pronouncements the practitioner does best to acquaint his patient with the nature of the abnormality give complete reassurance as to the present outlook request re-examinations three or four times annually but otherwise recommend a course of skillful neglect

Differential Diagnosis of

Hyperglycemic Glycosuria

Unlike hypoglycemic glycosurias (p 4406) hyperglycemic glycosurias are persistent unless the fundamental etiologic mechanism can be eradicated (hyperthyroidism and increased intracranial pressure) or controlled (dietary and insulin treatment of diabetes mellitus) Although the majority of hyperglycemic glycosurias occur in pancreatic diabetes they also may accompany other endocrinopathies as well as renal hepatic and neurologic disturbances

CLINICAL MANIFESTATIONS AND DIAGNOSTIC FEATURES

Hyperthyroidism	With tachycardia exophthalmos tremor loss of weight and elevation of B M R (p 1192) Note response to antithyroid drugs Remember that hyperthyroidism and diabetes mellitus often coexist
Hyperpituitarism	Acromegaly with characteristic overgrowth of bones of hands feet and face (p 1156) Pituitary basophilism (Cushing) with girdle obesity cutaneous striae hypertension and hypogonadism (p 1159) Get x rays of sella turcica Consult neurologist and neurosurgeon
Tumor of Adrenal Cortex	With manifestations of pituitary basophilism (p 1159) Refer to urologist for peri renal insufflation and x rays Consider surgery
Increased Intra Cranial Pressure	Particularly subarachnoid hemorrhage following head injuries or with brain tumors (p 1421) Consult neurologist and neurologic surgeon Consider exploratory craniotomy
Nephropathy	With marked depression of renal function particularly in advanced nephropathies involving glomeruli (p 2364) With combined symptoms of diabetes mellitus and evidences of acidosis both conditions may co exist
Hemochromatosis	In adult males exposed to metal in industry or by wine drinking (p 1976) Note pigmentation of skin (bronze diabetes) chemical tests for iron in skin enlargement of liver and atrophy of testes with manifestations of hypogonadism (p 2412)
VonGierke Disease (Glycogen Disease)	In children with enlargement of liver and spleen (p 1978) Note alternating hyperglycemia and hypoglycemia with or without ketosis
Diabetes Mellitus	With hyperglycemia decreased sugar tolerance and increased glycosuria following hyperalimentation (p 1246) Note favorable response to insulin (p 1255) and tendency to develop ketosis

MENINGOCOCCAL INFECTIONS

Principles of Diagnosis and Therapy

1 Meningococci may be grown from throat cultures of many healthy carriers (p 209) The organism also may invade and produce atypical or subclinical attacks of respiratory infection resembling the common cold or influenza As a result immune bodies are demonstrable in bloods of many who give no clear history of classical meningococcal infection

Least often patients suffer acute or chronic meningococcemia with its characteristic purpuric eruption (Fig 23 p 212) cerebrospinal meningitis with demonstrable gram negative intracellular cocci in cerebrospinal fluid (Fig 8 B p 47) and the syndrome of Waterhouse and Friderichsen in which manifestations of meningococcemia are associated with adrenocortical insufficiency (p 211)

2 While a natural active immunity seems to develop frequently efforts to stimulate artificial active immunity by means of meningococcus vaccine (Sherman) have never been successful

3 Despite discouraging prospects in active immunization curative treatment of meningococcal infection is an embarrassment of riches The organism is sensitive to penicillin sulfonamide aureomycin chlor amphenicol and streptomycin So potent are newly introduced anti biotics that antimeningococcus heterologous serum (once regarded as a most potent anti infective agent) already has been dropped from the approved list of the Council on Pharmacy and Chemistry of the Ameri can Medical Association

Practical Management

Immediate Care

1 Notify health authorities of the presence of the infection

2 Preferably transfer the patient to a hospital equipped for the care of the infected patient (p 67)

3 Protect exposed members of the family other contacts nursing attendants and medical staff with prophylactic chemotherapy Orally choose between daily doses of 2 gm of sulfadiazine or sulfamerazine with 1 teaspoonful of bicarbonate of soda or tablets of 250 000 units of crystalline potassium penicillin G given twice daily For preferred parenteral chemoprophylaxis make 3 daily deposits each of 300 000 units of crystalline procaine penicillin G in aqueous suspension

4 Have throat cultures made of contacts for detection of carriers To carriers give daily deposits each of 300 000 units of crystal line procaine penicillin G in aqueous suspension until two successive negative throat cultures have been reported

5 Because of potential gravity of meningococcal infections treat subclinical as well as classical meningococcal invasions with intensive combined antibiotic therapy Particularly during an epidemic regard any illness resembling the upper respiratory infection or influenza as

evidence of meningococcal invasion Institute therapy without awaiting bacteriological confirmation of clinical suspicions

6 In the days when penicillin supplies were short the majority of clinicians favored soluble sulfonamide as the agent of choice in the treatment of meningococcemia In these early experiences comparisons were made between adequate doses of sulfonamide and what are currently regarded as relatively inconsequential doses of penicillin (30 000 units every three hours)

7 The debate as to the favored preparation in the treatment of meningococcal infection need not concern the private practitioner Confronted with the challenge of treating an individual patient use both antibiotic agents and take advantage of their cumulative or synergistic actions

8 In milder infections particularly during an epidemic when major efforts must be devoted to the acutely ill oral therapy may be required For priming doses give two million units of crystalline potassium penicillin G (4 tablets each of 500 000 units) together with 2 gm each of sulfadiazine and sulfamerazine and a teaspoonful of bicarbonate of oda A few hours later start maintenance doses of 500 000 units of crystalline potassium penicillin G and 0 5 gm each of the soluble sulfonamides at 4 6 or 8 hour intervals depending on intensity of infection and patient response

9 In more severe infections set up intravenous drip For the priming dose infuse 1 million units of crystalline potassium penicillin G in physiologic saline or molar lactate solution As soon as this has been introduced add to the drip 2 5 gm each of sodium sulfadiazine and sodium sulfamerazine dissolved in at least another 200 cc of diluent

10 If there are evidences of adrenocortical insufficiency in addition to penicillin sulfonamide introduce 250 to 500 cc of plasma Make an intramuscular injection of 20 mg of desoxycorticosterone acetate in oil if cortone or ACTH cannot be obtained

11 Whether antibiotics are given orally or intravenously prescribe prophylactic antihistamine using 200 mg daily of pyribenzamine or benadryl If the patient is unable to swallow introduce into the intravenous drip or intramuscularly 5 cc of 1% benadryl

12 If diagnosis is in doubt perform lumbar puncture preferably after the priming dose of antibiotic has been introduced The post treatment tap when blood antibiotic levels are at their height favors development of high titers of antibiotic in cerebrospinal fluid

13 As to intrathecal medication there is currently general agreement that this cumbersome route of administration is contrary to the best interests of the patient

Hoyne (Ill M J 94 295 1949) lists eleven objections to intrathecal therapy They include discomfort and pain to the patient tendency to produce opisthotonos uncertainty that the amount of remedy is sufficient to control infection repeated spinal punctures increase chances of producing secondary infection possible injury to intervertebral disks which may result in permanent disability hemorrhage or throm

bosis of vessels resulting in degenerative changes in the spinal cord, production of adhesions blocks and hydrocephalus slower recovery greater likelihood of relapse failure to reduce fatality rates and theoretical fact that the procedure is unscientific and has no advantages though it is accompanied by hazards

In similar vein Wilson Rupp and Wilson (J A M A 140 1076 1949) state their opinion that there is no doubt that intrathecal injections of drugs anesthetics and antibiotics produce neurologic complications in many cases The neurologic residuals are often serious permanent disabling and unamenable to any known therapy These authors go on to say that when adequate spinal fluid concentrations of an agent can be obtained following systemic administration as with the sulfonamide compounds and penicillin intrathecal administration is truly meddlesome mischief and is strictly contraindicated Since the usual direction of the flow of cerebrospinal fluid is from the ventricles to the subarachnoid space it is doubtful that an appreciable quantity of any medicament introduced into the lumbar sac diffuses to any extent through the subarachnoid pathways Probably any benefit from therapeutic substances injected intrathecally occurs only after absorption into the blood stream has occurred Thoughtful consideration of these facts may avoid many tragic neurologic sequelae without depriving the patient of every chance of maximum therapeutic aid

Continuing Care (Favorable Course)

1 Maintain antibiotic levels by continued administration of sulfonamide and penicillin If course is favorable discontinue intravenous drip Give sulfonamide orally and penicillin by intramuscular injection Prescribe daily doses of 1 5 to 2 gm each of sulfadiazine and sulfamerazine with a teaspoonful of bicarbonate of soda Deposit intramuscularly 600 000 units of crystalline procaine penicillin G in aqueous suspension

2 Continue antihistamine for at least two weeks after last dose of antibiotic

Continuing Care (Unfavorable Course)

1 Maintain intravenous drip Increase daily dose of penicillin as high as 25 million units of crystalline potassium penicillin G If there are no evidences of sulfonamide toxicity by clinical examination urine analysis and blood counts repeat priming dose of sodium sulfadiazine and sodium sulfamerazine twice or thrice daily

2 If patient is sulfonamide sensitive or manifestations of toxicity develop or if there is no response to combined sulfonamide/penicillin substitute or add aureomycin Introduce 200 to 500 mg of aureomycin hydrochloride (for intravenous use) in the diluent of 0 75% sodium carbonate provided by the manufacturer

3 If patient is penicillin sensitive continue with sulfonamide and supplement with aureomycin as above

4 As a substitute for aureomycin hold streptomycin in reserve Meningococci are sensitive to this antibiotic but to a lesser degree than

to penicillin aureomycin or sulfonamide Deposit 1 to 2 gm intramuscularly for priming dose Continue 0 5 to 1 gm at 6 8 or 12 hour intervals as indicated

5 If clinical picture is predominantly that of adrenocortical insufficiency institute treatment for the Addisonian crisis (p 4159)

6 Since meningococcal infections tend to relapse continue antibiotics for at least three to five afebrile days

MENSTRUATION, OVULATION AND IMPREGNATION

[Temperature Variations Due to]

In addition to individual and diurnal variations (p 3484) readings of body temperature reveal cyclic fluctuations during active female sexual life To obtain a suitable graph the woman records daily rectal readings on arising each morning for a span of at least one complete month

Temperature Curves of Normal Menstrual Cycles

During the normal menstrual cycle there is a characteristic and individual diphasic curve con isting of a lower postmenstrual phase a low to high shift at ovulation and a higher premenstrual level The postmenstrual phase which lasts for about two weeks spans the period between cessation of flow and ovulation Ovulation is characterized by a low to high shift approximating 0 4–0 8 F This higher level is sustained during the premenstrual phase which terminates just before or at the time of the next bleeding

Temperature Curve in Anovulatory Menstruation

The woman who fails to ovulate for whatever rea on displays a monophasic temperature graph during her menstrual cycle there is no demonstrable low to high shift premenstrual and postmenstrual phases are indistinguishable

Temperature Curve of Pregnancy

When fertilization is successfully accomplished the postmenstrual phase is unmodified the ovulatory low to high shift occurs as previously but the premenstrual elevation persists for sixteen days or more This latter phenomenon in association with amenorrhea provides earliest suggestion of pregnancy and constitutes what has been facetiously termed the poor man s rabbit test

Practical Considerations

In practice unfortunately basal temperature graphs are not as easily interpreted as the text suggests Many variables impinge to create confusion so that it is often necessary to continue ob ervations for several months in order to establish a definitive pattern

Some technical discrepancies may be avoided if temperatures are

bosis of vessels resulting in degenerative changes in the spinal cord production of adhesions blocks and hydrocephalus slower recovery greater likelihood of relapse failure to reduce fatality rates and theoretical fact that the procedure is unscientific and has no advantages though it is accompanied by hazards

In similar vein Wilson Rupp and Wilson (J A M A 140 1076 1949) state their opinion that there is no doubt that intrathecal injections of *drugs anesthetics and antibiotics produce neurologic complications in* many cases The neurologic residuals are often serious permanent disabling and unamenable to any known therapy These authors go on to say that when adequate spinal fluid concentrations of an agent can be obtained following systemic administration as with the sulfonamide compounds and penicillin intrathecal administration is truly meddlesome mischief and is strictly contraindicated Since the usual direction of the flow of cerebrospinal fluid is from the ventricles *to the subarachnoid space it is doubtful that an appreciable quantity* of any medicament introduced into the lumbar sac diffuses to any extent through the subarachnoid pathways Probably any benefit from therapeutic substances injected intrathecally occurs only after absorption into the blood stream has occurred Thoughtful consideration of these facts may avoid many tragic neurologic sequelae without depriving the patient of every chance of maximum therapeutic aid

Continuing Care (Favorable Course)

1 Maintain antibiotic levels by continued administration of sulfonamide and penicillin If course is favorable discontinue intravenous drip Give sulfonamide orally and penicillin by intramuscular injection Prescribe daily doses of 1 5 to 2 gm each of sulfadiazine and sulfamerazine with a teaspoonful of bicarbonate of soda Deposit intramuscularly 600 000 units of crystalline procaine penicillin G in aqueous suspension

2 Continue antihistamine for at least two weeks after last dose of antibiotic

Continuing Care (Unfavorable Course)

1 Maintain intravenous drip Increase daily dose of penicillin as high as 25 million units of crystalline potassium penicillin G If there are no evidences of sulfonamide toxicity by clinical examination urine analysis and blood counts repeat priming dose of sodium sulfadiazine and sodium sulfamerazine twice or thrice daily

2 If patient is sulfonamide sensitive or manifestations of toxicity develop or if there is no response to combined sulfonamide/penicillin substitute or add aureomycin Introduce 200 to 500 mg of aureomycin hydrochloride (for intravenous use) in the diluent of 0 75% sodium carbonate provided by the manufacturer

3 If patient is penicillin sensitive continue with sulfonamide and supplement with aureomycin as above

4 As a substitute for aureomycin hold streptomycin in reserve Meningococci are sensitive to this antibiotic but to a lesser degree than

MERCURY

As an anti infective agent mercury the great specific of the Middle Ages and the Restoration period persists only as a local or topical application It is obsolete as an anti syphilitic and has even been replaced as a pediculocide Currently its principal systemic use is for diuresis (p 4305)

Toxicity

See Mercurialism (p 765)

Antidote

See BAL (p 4251)

METHENAMINE

[Hexamethylenamine Formin Urotropin]

Although methenamine remains a Council approved product it is a usele..s and obsolescent anti infective agent and urinary antiseptic (p 4626)

Available Products

Methenamine (Abbott) Tablets 0 3 and 0 5 gm
Urotropin (Schering) Tablets 0 3 and 0 5 gm

Therapeutics

Methenamine should not be used despite its continued exploitation As a urinary antiseptic in an acid medium mandelic acid is prefer able for all purpose urinary antisepsis urotropin cannot compare with sulfonamide streptomycin aureomycin and chloramphenicol

MOLLUSCUM CONTAGIOSUM

Molluscum contagiosum is a cutaneous virus infection (p 3287) which is too insignificant to warrant systemic therapy with aureomycin or chloramphenicol despite the fact that either or both of these anti biotics should prove successful in its management (Fig 70 D and E p 436)

MONILIASIS

[Thru..h Perleche Bronchomoniliasis 'Thresher s Lung]

General Principles of Diagnosis and Therapy

1 Cutaneous and mucosal moniliasis respond to persistent local therapy Systemic moniliasis especially broncho respiratory (Fig 81 p 503) is less easily attacked by anti infective agents

taken at exactly the same time each morning before the woman has risen from bed and evacuated rectum and bladder Other vagaries arise from intercurrent infection or interpolation of any of numerous factors responsible for aseptic pyrexia (p 23) In some instances fluctuations are due to imponderables and at least three or four monthly cycles require registration before definitive conclusions are merited

When there can be eliminated fluctuations resulting from factors other than those concerned with the physiology of menstruation the following conclusions are justifiable from basal temperature readings taken throughout the menstrual cycle

1 A monophasic temperature pattern suggests that the woman has not ovulated at least during the period of observation She may be regarded at least temporarily as infertile due to hormonal deficiency involving anterior pituitary and/or gonadal secretions

2 A diphasic curve with a lower postmenstrual level and a higher premenstrual phase suggests that the woman has ovulated at the time of the low to high shift She may be regarded as fertile so far as hormonal factors are concerned

3 The low to high shift separating postmenstrual from premenstrual phases (particularly if it occurs in the middle of the cycle and is otherwise inexplicable) probably indicates ovulation and onset of the period of fertility or vulnerability This brief span of eighteen to thirty six hours presents maximum opportunity for impregnation

Those desirous of progeny are advised to have intercourse immediately after the low to high shift

Those who must or would avoid impregnation are advised to refrain from intercourse unless they practice contraception (p 2502)

4 Except for the day preceding the low to high shift and for a span of seventy two to ninety six hours thereafter the woman may be regarded as temporarily infertile Despite potent insemination impregnation is unlikely during the safe period preceding and following the low to high shift

Those who must refrain from childbearing need not necessarily use contraceptive devices at these times

5 Maintenance of the pre menstrual elevation for approximately fourteen days with a fall to the postmenstrual level (particularly if associated with menstrual bleeding) suggests ovulation but not impregnation

6 Persistence of the premenstrual elevation following the low to high ovulatory shift for sixteen days or more (particularly if associated with amenorrhea) suggests the woman has both ovulated and impregnated

7 Conversion of the anovulatory monophasic temperature pattern to the ovulatory diphasic curve (particularly during concurrent hormonal therapy) indicates a restitution to normal

8 The infertile woman who presents a normal diphasic curve or a monophasic curve which has been converted to the diphasic pattern as the result of therapy may be regarded as barren due to factors other than hormonal deficiency (pp 2419 and 2492)

MORPHINE DERIVATIVES AND SYNTHETIC SUBSTITUTES

The field of analgesia has been enriched by addition of at least one new opium derivative and several synthetic substitutes whose properties supplement and in certain instances substitute for preparations listed in Table 220 (p 3854) Certain of these products prepared by German scientists bear several names To avoid understandable confusion the accompanying table has been prepared (p 4416)

1 *Dihydrocodeinone Bitartrate N N R* (mercodinone hycodan bitartrate dicodid) shares with codeine the property of being the most effective cough remedy It resembles codeine in that it is habit forming and possesses the undesirable side effects of causing constipation and difficulty in urination

2 *Meperidine Hydrochloride* (Lonipecaine Hydrochloride or Demerol Winthrop) is a synthetic resembling atropine in its chemical structure With methadone meperidine shares the position of preparation of choice in oral and parenteral control of pain It depresses the central nervous system with a morphine like effect simultaneously as opposed to morphine demerol depresses smooth muscle in a manner simulating that of atropine hence it is free from untoward morphine side effects of constipation and disturbances of urination Oral doses of 100 mg of demerol elevate the pain threshold within fifteen minutes producing satisfactory analgesia which lasts for several hours Because of its atropine like spasmolytic action visceral pain is relieved more effectively than cerebral or neurogenic pain Comparative studies indicate that 50 mg injected intramuscularly are more potent than 22 mg of codeine and 5 mg of morphine In conditions associated with spasm (pregnancy asthma biliary urinary or gastro-intestinal colic) demerol is particularly effective

Except for atropine like drying of the mouth with flushing of the face demerol has no significant side effects except for occasional nausea and vomiting Its limitations include feeble antitussive effect, tendency to habituation and unavailability for intravenous use

3 *Methadone hydrochloride* is a synthetic marketed as methadone (Abbott Massengill) adanon (Winthrop) and dolophine (Lilly) Its chemical constitution is 6-dimethylamino 4 4-diphenyl 3-heptanone hydrochloride Methadone shares with meperidine the position of analgesic of choice It does not have the atropine like qualities of meperidine and it is not a sedative making it less useful for relief of nocturnal pain but more useful for analgesia during waking hours Methadone has definite addiction liability its effect on smooth muscle is relatively negligible neither producing contraction as does morphine nor relaxation as does meperidine In contrast to meperidine methadone has a satisfactory antitussive action though not as effective as dihydrocodeinone bitartrate or codeine itself

Dose for dose methadone is more potent than meperidine but it has proportionately greater toxicity In general it may be assumed that 5 mg of methadone compares with 50 mg of meperidine whether given orally or parenterally Like meperidine methadone is not available for intravenous injection

2 For cutaneous moniliasis (p 3301) apply 1 to 2% gentian violet in 70% alcohol every six to twelve hours Onychia and paronychia require 3% solutions with soakings thrice daily in 1 4000 potassium permanganate During therapy order patients to keep hands out of dish water particularly

3 Mucosal moniliasis occurs orally (thrush perleche) and vaginally For the former (p 503) use alkaline mouth washes paintings of 1% gentian violet gargles of 1 1000 gentian violet and applications of 20% sodium caprylate (adjusted to *p*H 7 4) thrice daily

4 Vaginal moniliasis (p 2598) is resistant to therapy unless measures of general hygiene are followed the patient avoids soiling of vulva with feces wiping anus from before backward rather than forward the husband submits to applications of 2% gentian violet to penis and foreskin and must agree to circumcision if necessary

Locally the vagina is painted with 1% aqueous or glycerine extract of gentian violet thrice daily If unsuccessful 10% jelly of sodium caprylate (p 4592) 3% ricinoleic acid in tragacanth casea jell and allantoin vaginal cream (p 4592) are tried

5 For systemic moniliasis successful treatment of meningitis has been reported with streptomycin using 0 5 gm intramuscularly every four hours and 25 to 50 mg intrathecally once daily Despite this success in a single instance the Council on Pharmacy and Chemistry of the American Medical Association 1947 is unimpressed and avers additionally that penicillin and sulfonamides are useless

6 Bronchomoniliasis or thresher s lung appears to respond to oral doses of potassium iodide (p 4377) inhalations of ethyl iodide (p 4378) *and injections of hyperimmune rabbit serum*

MORAX AXENFELD CONJUNCTIVITIS

[Angular Conjunctivitis]

General Principles of Diagnosis and Therapy

1 The diplobacillus responsible for Morax Axenfeld conjunctivitis is sensitive to aureomycin

2 For local application use 3% ointment of aureomycin hydro chloride on conjunctivas and lids Every two hours instill 2 to 4 drops of aureomycin ophthalmic solution prepared by adding 5 cc of diluent (supplied by manufacturer) to vial containing 25 mg of antibiotic This solution remains stable for two days if kept in the refrigerator

3 Alternatively instill solutions of 0 05 to 0 5% zinc sulfate Zinc salts inhibit proteolytic ferment secreted by the organism

4 If there are systemic manifestations or the infection appears resistant and productive of local damage of more than mild severity supplement with oral doses of aureomycin or chloramphenicol giving 50 mg per kilogram of body weight per day *(2 capsules each of 250 mg* every six hours)

7 For pre anesthetic medication we prefer meperidine to metha done The former has sedative effect the latter none

8 For concurrent relief of pain and muscle spasm there is no present rival to meperidine Methadone is indifferent in its action on smooth muscle older morphine derivatives and substitutes increase spasm with resultant constipation retention of urine and increased difficulty in spastic conditions such as pregnancy bronchial asthma and colics The single exception to this is papaverine used in much larger than recommended doses (60 to 120 mg)

9 For comparative addiction liability score morphine and dihy dromorphinone hydrochloride (dilaudid) highest at 8 metopon at 7 meperidine hydrochloride (demerol) methadone hydrochloride (adanon methadone and dolophine) next at 5 and codeine least at 3 (Lobel et al J A M A 138 1025 1948)

10 For comparative analgesic efficacy of single doses rate metopon (6 mg) as most efficacious followed by morphine (10 mg) meperidine demerol (100 mg) methadone (5 to 10 mg) and codeine (30 mg)

11 For comparative sedation of single doses rate morphine first followed by meperidine metopon methadone and codeine (Lobel et al loc cit)

12 For the comparative duration of analgesic action in hours rate methadone first with a span of four to ten hours morphine metopon and codeine next with four hours and meperidine last with three hours using doses above mentioned

MUMPS

[Epidemic Parotitis]

General Principles of Diagnosis and Treatment

1 In infancy and childhood mumps is usually confined to inflam mation of the parotid glands (p 480) In the adult however the con cept of simple epidemic parotitis is far too limited In Eagle s experience epididymo-orchitis occurred in 25 per cent meningo encephalitis in 2 6 per cent presternal edema in 1 2 per cent and three instances each of pancreatitis and myocarditis were observed in 1664 adult patients When routine lumbar punctures were made Brown and associates (A J Med Sci 215 440 1948) found a pleocytosis in 34 per cent although only 8 per cent had clinical evidences of meningeal irritation

2 These complications together with increasing recognition that mumps meningoencephalitis may occur without patent parotitis has led to increasing efforts to prevent the disea e and provide active treatment once complications have developed

3 The diagnosis of mumps is usually obvious Where there is doubt antigen is available for skin testing and complement fixation reactions may be done on serum

OPIUM DERIVATIVES AND SYNTHETIC SUBSTITUTES

Product	Available Preparations
Adanon (Winthrop)	See Methadone N N R.
Amidone	Previous brand name for Methadone
An 148	Previous brand name for Methadone
Demerol (Winthrop)	See Meperidine Hydrochloride N N R
Diaminon	Previous brand name for Methadone
Dihydrocodeinone Bitartrate N N R.	Tablets 5 mg
	Syrup 1 cc = 1 mg
	Mercodinone (Merrell) hycodan bitartrate (Endo) and Dicodid (Bilhuber) Probably the most useful anti tussive remedy
Dolantin	Previous brand name for Meperidine
Dolophine (Lilly)	See Methadone N N R
Hycodan Bitartrate (Endo)	See Dihydrocodeinone Bitartrate N N P
IG 10820	*German identification of methadone*
Isonipecaine	See Meperidine Hydrochloride
Meperidine Hydrochloride N N R	Oral tablets 50 mg
(Isonipecaine Demerol) Winthrop	Hypodermic tablets 50 and 100 mg
	Ampuls 1 cc = 50 mg
	Vials for hypodermic use containing 30 cc of which 1 cc = 50 mg
	Elixir 1 cc = 25 mg
	See also p 4415
Mercodinone (Merrell)	See Dihydrocodeinone
Methadone Hydrochloride N N R	Oral tablets 2 5—5—7 5— and 10 mg
	Elixir 1 cc = 1 mg
	Syrup 30 cc = 10 mg
	Ampuls for hypodermic use 1 cc = 5–10 mg
	Marketed as methadone (Abbott Massengill) adanon (Winthrop) and dolophine (Lilly)
	A synthetic which with meperidine is the preparation of choice for oral and parenteral analgesia See p 4415
Methyl Dihydromorphine	See Metopon
Metopon	Capsules of 3 mg For investigational use only as oral analgesic in self treatment of pain of malignancy
	Very similar to dihydromorphinone or dilaudid N N R. (p 3855)
Miodine	Previous brand name for methadone
Pethidine	Previous brand name for meperidine hydrochloride (Demerol)

4 *Metopon* is a preparation of methyl dihydromorphinone Originally introduced for investigational use only as an oral analgesic for self treatment of intractable pain in malignancy metopon has no significant advantage over meperidine or methadone

5 Our personal choices for antitussive action are dihydrocodeinone bitartrate methadone and codeine in that order

6 Our personal preferences for oral analgesia are meperidine for nocturnal pain and meperidine or methadone for diurnal pain For subcutaneous injection we have the same preferences for intravenous use we employ dihydromorphinone hydrochloride (dilaudid Bilhuber) or morphine sulfate itself

The accompanying chart is intended for clarification of the pharma cology of muscle since correct use of muscle relaxant drugs is of symptomatic value in conditions as varied as hypertension traumatic and diseased conditions of peripheral vessels migraine asthma intes tinal biliary and urinary colics thrombophlebitis frostbite Raynaud s disease the tremors of parkinsonism multiple sclerosis hepatolenti cular degeneration and arteriosclerosis convulsions of all types and muscle pain in tetanus poliomyelitis and rabies

For direct action on smooth muscle the practitioner has at his dis posal nitrites and thiocyanates each of which has serious side effects that all but nullify their usefulness for inhibition of autonomic stimu lants depending on motor innervation there are available adreno lysins and atropine like drugs which depress or paralyze nerve endings of the cranio sacral division of the involuntary nervous system for stimulation of autonomic inhibitors the patient may be given adren ergens such as epinephrine to relax bronchospasm as in asthma or cholinergins such as neostigmine to alleviate spasm and tremors in cerebral palsy

MUSCLE RELAXANTS

Adrenalin

Commercial brand of epinephrine (p 3877) Useful only in relaxing smooth muscle innervated by the thoracolumbar division of the involuntary nervous system as particularly seen in bronchial asthma (p 2101)

Adrenergens

Useful only in relaxing smooth muscle innervated by the thoracolumbar division of the involuntary nervous system (p 3877)

Adrenolysins

See sympatholysins

Amphetamine

Marketed as benzedrine an adrenergen (p 3882)

Antihistamines

Somewhat useful in the treatment of tremors of striated muscle (p 2882) May supplement more potent preparations such as artane

Artane

Commercial brand (Lederle) of trihexyphenidyl marketed in tablets of 2 and 5 mg Artane is useful in the treatment of involuntary tremors of the extremities and in muscle spasticity particularly as seen in parkinsonism (p 1505) Give 2 mg after meals and a fourth do e at bedtime if necessary Increase to 5 mg if needed, provided that side effects of nausea or blurring of vision do not occur

Atropine

Used with other depressants of the cholinergic system to relieve muscle tremors and spasticity as in parkinsonism (p 3875) Side effects of dryness of mouth and pupillary dilatation add to patient-discomfort

Banthine

Powerful new anticholinergin particularly valuable in peptic ulcer

4 At least two efforts at vaccine therapy (a formalized mumps vaccine and a vaccine of attenuated virus) have been attempted without signal success Neither effort has been sufficiently successful to warrant widespread or commercial introduction

5 Specific therapy for prevention and treatment of complications also has lagged Neither human convalescent serum nor gamma globulin obtained from normals accomplished much in the way of prophylaxis or therapy However gamma globulin derived from human volunteer convalescents and given in intramuscular injections of 20 cc has considerable promise This amount is the equivalent of 200 cc of normal gamma globulin and 400 cc of human convalescent serum

6 Prevention and treatment of orchitis and oophoritis al o have been attempted with hormonal therapy Oral administration of diethyl stillbestrol in doses of 5 mg daily for three to five days in the male has been suggested By this means the incidence of orchitis in the adult was reduced from 20 per cent to less than 4 per cent Evaluation of hormonal therapy in the female offers greater difficulties but it is suggested that it be carried out with larger doses of testosterone (25 mg daily for three to five days)

7 Of antibiotics sulfonamide and penicillin are without value Chloramphenicol and aureomycin however merit trial since they have proven useful in other virus infections

Practical Management

1 Institute measures for care of the infected patient (p 64)

2 For the male order 5 mg diethylstilbestrol daily for three to five days for the female 25 mg testosterone propionate daily for three to five days

3 If gamma globulin can be obtained from recently convalescent human volunteers deposit 20 cc intramuscularly

4 For severe or complicated infections prescribe aureomycin or chloramphenicol in doses of 50 mg per kilogram of body weight per day (3 5 gm for average adult weighing 150 pounds)

MUSCLE RELAXANTS

The pharmacology of muscle is as complicated as it is important The practitioner is required to differentiate between striated and smooth muscles since each responds differently to drugs additionally some smooth muscles receive motor innervation from the cranio sacral division of the involuntary nervous system while others are encouraged to contract through the thoracolumbar division The situation with striated muscles is even more difficult since these structures are innervated both by voluntary and involuntary nervous systems In consequence muscle relaxation may be accomplished by drugs that act directly on muscle by inhibitors of autonomic stimulants and by depressors of autonomic inhibitors

MUSCLE RELAXANTS (*Continued*)

Cholinergins

Despite enthusiastic introduction, of negligible value in relief of spasticity and tremor of cerebral palsy

Cholinergen Depressants

See atropine etc (p 3875)

Chondrodendron Tomentosum Extract Purified N.N.R.

An aqueous preparation containing the therapeutically effective constituents of crude curare and marketed as d tubocurarine chloride (Abbott, Squibb) and intocostrin (Squibb) Curare an arrow poison, blocks myoneural transmission to skeletal muscle in therapeutic doses in larger doses it may depress ganglionic transmission in the involuntary nervous system. Unfortunately preparations of curare are also toxic and may produce hazy vision, difficulty in talking and swallowing, weakness of eye muscles jaw neck and leg muscles followed by ptosis relaxation of the muscles of the neck spine legs and abdomen terminal paralysis of the diaphragm, and cessation of respiration. Physostigmine and neostigmine are pharmacological antidotes and must be held available any time that a curare preparation is injected. Curare is distinctly a specialist drug It may be used, under institutional conditions when means for artificial respiration and maintenance of the airway are at hand, for supplementation in anesthesia to diminish the violence of convulsions in shock therapy and to diminish muscle spasm and pain in poliomyelitis and tetanus For the practitioner less toxic spasmolytics (tolserol, caramiphen and artane) are preferable

Curare

See purified chondodendron tomentosum extract above

Dibenamine

Dibenamine one of the first isolated adrenolysins has the formula N N-dibenzyl b-chloroethylamine Dibenamine is not commercially available but may prove of later value since the effects of a single injection persist for thirty six to ninety six hours Resting blood pressures and cardiac rates fall in early and moderately advanced essential hypertension but not in patients in malignant phases of the disease or in those who are normotensive Unfortunately dibenamine produces a transient repetitive temporal hallucination or reduplicated paramnesia with the phenomenon of deja vu (p 1299)

Dihydroergotamine or Dihydroergocornine

A potent sympatholytic agent commercially available in ampuls containing 1 cc (Sandoz) For use in prevention and treatment of migraine and for non obstetrical indications particularly reduction of essential hypertension. Introduce subcutaneously or intramuscularly in doses of 1 to 2 cc provided that side reactions are not encountered (nausea vomiting muscular weakness angiospasm, etc)

d Tubocurarine

See Chondrodendron Tomentosum

Epinephrine

The first and most powerful adrenergen or sympathomimetic preparation (p 3877) Useful only in relaxing smooth muscle spasm when there is motor innervation by the thoracolumbar division of the involuntary nervous system, as in asthma

Ergotamine

See cafergone above

MUSCLE RELAXANTS (*Continued*)

Benodaine

Benodaine hydrochloride (Merck) is supplied in 10 cc ampuls each of which contains 20 mg of the drug (0 2% solution in saline) Commercial benodaine is 2 (1 piperidylmethyl) 1 4-benzodioxane hydrochloride Benodaine is an adrenolysin, decreasing and then abolishing the action of epinephrine on blood pressure Currently it is used solely to make the diagnosis of hypertension due to epinephrine producing tumors of the adrenal medulla (pheochromocytomas) and of extra-adrenal chromatin tissues (paragangliomas) Injected intravenously into the patient suffering from either of these tumors there is a brief but dramatic decrease in blood pressure which does not occur in hypertension due to any other cause Since untoward effects with intravenous benodaine may be very serious (tachycardia flushing palpitation nervousness hyperpnea headache dizziness substernal pressure and precordial distress) the technic of injection requires scrutiny under institutional conditions Determine surface area of the body from basal metabolism chart Inject intravenously 10 mg of benodaine per square meter of body surface (average dose for adult weighing 150 lbs equals 15 to 20 mg or 7 5 to 10 cc of commercially available 0 2% olution) The patient is required to be supine throughout injection and for a period of at least a half hour thereafter Becau e of toxic reactions it is best to give the drug well diluted in an intravenous drip lowly introduced A positive response consi ts in a significant fall in blood pressure that occurs within a few moments with a return to pre injection level in about fifteen minutes Except in the presence of the epinephrine producing tumor the blood pressure is unaffected or shows a transitory rise

Benzazoline Hydrochloride

Commercially available as priscol (Ciba)

Benzedrine

Brand of amphetamine a sympathomimetic preparation or adrenergen (p 3882)

Cafergone

An extremely useful commercial preparation Each tablet contains 1 mg of ergotamine tartrate and 100 mg of caffeine Ergotamine is a sympatholytic preparation of almost specific value in the treatment of migraine (p 1508) In synergistic combination with caffeine ergotamine appears to be as useful when given orally as when injected Hence it has great practical value for self treatment of attacks Suggest an average initial dose of 2 tablets at onset of symptoms Give an additional dose at 30 minute intervals until a total of 6 has been ingested unless relief occurs sooner Ergotamine and allied preparations are contraindicated in the presence of peripheral vascular disease angina impaired renal or hepatic function and pregnancy

Caramiphen Hydrochloride

Spasmolytic synthetic available commercially as panparnit (parpanit) marked in sugar coated tablets containing 12 5–50 mg (Geigy) Chemically caramiphen is diethylaminoethyl 1 phenylcyclopentane 1 carboxylate hydrochloride It appears to block proprioceptive impulses arising in muscles and joints thus diminishing intensity of reflexes that produce muscle rigidity in parkinsonian syndrome (p 1505) Treatment is inaugurated with 12 5 mg 5 times daily The daily dose is increased gradually to tolerance up to 90 to 600 mg with an average of 200 to 400 mg Toxic manifestations include dizziness weakne s dryness of mouth blurring of vision and diplopia In the hands of objective inve tigators caramiphen gave subjective improvement in approximately half of the patients with parkinsonism as well as others with idiopathic and arteriosclerotic tremors dystonia and hepatolenticular degeneration (Sciarra et al J A M A 141 1226 1949) Unfortunately initial subjective improvement did not persist and the final evaluation of caramiphen was disappointing with prolongation of improvement in only 7 per cent, offset by 86 per cent with untoward side effects

MUSCLE RELAXANTS (*Continued*)

Cholinergins

De pite enthusiastic introduction of negligible value in relief of spasticity and tremor of cerebral palsy

Cholinergen Depressants

See atropine etc (p 3875)

Chondrodendron Tomentosum Extract Purified N N R.

An aqueous preparation containing the therapeutically effective constituents of crude curare and marketed as d tubocurarine chloride (Abbott Squibb) and intocostrin (Squibb) Curare an arrow poison blocks myoneural trans mission to skeletal muscle in therapeutic doses in larger doses it may depress ganglionic transmission in the involuntary nervous system Unfortunately preparations of curare are also toxic and may produce hazy vision difficulty in talking and swallowing weakness of eye muscles jaw neck and leg muscles followed by ptosis relaxation of the muscles of the neck spine legs and abdomen terminal paralysis of the diaphragm and cessation of respiration Physostigmine and neostigmine are pharmacological antidotes and must be held available any time that a curare preparation is injected Curare is dis tinctly a specialist drug It may be used under institutional conditions when *means for artificial re piration and maintenance of the airway are at hand,* for supplementation in anesthesia to diminish the violence of convulsions in shock therapy and to diminish muscle spasm and pain in poliomyelitis and tetanus For the practitioner less toxic spasmolytics (tolserol caramiphen and artane) are preferable

Curare

See purified chondodendron tomentosum extract above

Dibenamine

Dibenamine one of the first isolated adrenolysins has the formula N N dibenzyl b chloroethylamine Dibenamine is not commercially available but may prove of later value since the effects of a single injection persist for thirty six to ninety six hours Resting blood pressures and cardiac rates fall in early and moderately advanced essential hypertension but not in patients in malignant phases of the disease or in those who are normotensive Unfortunately dibena mine produces a transient repetitive temporal hallucination or reduplicated paramnesia with the phenomenon of deja vu (p 1299)

Dihydroergotamine or Dihydroergocornine

A potent sympatholytic agent commercially available in ampuls containing 1 cc (Sandoz) For use in prevention and treatment of migraine and for non obstetrical indications particularly reduction of essential hypertension Intro duce subcutaneously or intramuscularly in doses of 1 to 2 cc provided that side reactions are not encountered (nausea vomiting muscular weakness angiospasm et)

d Tubocurarine

See Chondrodendron Tomentosum

Epinephrine

The first and most powerful adrenergen or sympathomimetic preparation (p 3877) Useful only in relaxing smooth muscle spasm when there is motor innervation by the thoracolumbar division of the involuntary nervous system as in asthma

Ergotamine

See cafergone above

MUSCLE RELAXANTS (*Continued*)

Etamon

A commercial preparation of tetraethylammonium chloride (Parke Davis) marketed in 20 cc vials of which each cc contains 100 mg The average dose injected intramuscularly is 10 to 12 cc not to exceed a total dose of 20 mg per kilogram of body weight (14 cc for average adult weighing 150 lbs) Intravenously smaller doses are advised approximating 1 to 5 cc but not exceeding 7 mg per kilogram of body weight (5 cc for average adult weighing 150 lbs) Etamon blocks nerve impulses of autonomic ganglia including both sympathetic and parasympathetic impulses Clinically the action of the drug may be compared to an extensive non surgical sympathectomy Following parenteral injection there is an abrupt fall in both systolic and diastolic blood pressures with an increase in peripheral blood flow Simultaneously gastric secretion is reduced gastric motility is increa ed and there may be retention of urine in the bladder due to spasm of the sphincter The pupils dilate accommodation is lost and the patient complains of drowsiness and an acid metallic taste of the mouth with peculiar hypere thesias over the entire body (sensations of pins and needles) The fall of blood pressure lasts fifteen minutes and there is a return to normal within twenty minutes though the patient may still note postural hypotension Clinically etamon has been used to provide an autonomic blockade in thromboangiitis obliterans lymphedema frost bite and traumatic conditions of the extremities in which the circulation is impaired At least one fatal experience with 230 mg of etamon has been observed

Gynergen

See cafergone

Intocostrin

See chondrodendron tomentosum extract above

Isonorin

A sympathomimetic amine particularly valuable when taken orally or by instillation in bronchial asthma (p 4270)

Isuprel

Same as above

Lissephen

Abbott brand of tolserol described below

Mephenesin

Abbott brand of tolserol described below

Myanesin

Engli h brand name for tol erol described below

Neostigmine

See cholinergins

Nitrites

Transitory relaxation of smooth muscle by direct action without neurogenic intervention U eful for transitory effects in angina (p 3892)

Oranixon

A synthetic with the chemical formula 3-ortho toloxy 1 2 propanediol Marketed in compressed tablets of 250 mg and an elixir of which one teaspoonful contains 400 mg (Organon) 4 to 5 tablets daily or 2 to 3 teaspoonfuls of elixir given three or four times daily promote muscular relaxation, relieve spasm of voluntary muscle and produce some analgesia Oranixon has been used for control of muscle spasm in parkinsonism (p 1505) hemiplegia and cerebral diplegia

MUSCLE RELAXANTS (*Continued*)

Panparnit (Parpanit)

See caramiphen above

Priscol

Priscol (benzazoline hydrochloride) is an adrenolytic and sympatholytic agent, marketed in tablets each of which contains 25 mg (Ciba) The dose is 1-2 tablets taken 5-6 times daily unless untoward manifestations develop Priscol has been used to produce vasodilatation and relieve angiospasm in intermittent claudication, thromboangiitis obliterans thrombophlebitis frostbite and Raynaud s disea e Large doses produce transitory faintness or syncope with orthostatic hypotension Untoward manifestations may be relieved by use of a sympathomimetic such as epinephrine or amphetamine

Scopolamine

An atropine like preparation useful in control of tremor in parkinsonism (p 3875) Side reactions similar to atropine with additional amnesia and other disturbances of cerebration Yields preference to artane caramiphen and tolserol

Sympatholysins

Sympatholysins or adrenolysins block the action of sympathomimetic preparations such as epinephrine Though Council approval has been given to none of presently available sympatholysins benodaine dibenamine etamon and priscol are available for experimental use or commercial purchase as elsewhere described in this chart.

Sympathomimetic Amines

Preparations with epinephrine like action as described above (p 3872)

Tea

See etamon.

Tetraethylammonium Chloride

See etamon

Thiocyanate

Advocated for direct depression of smooth muscle particularly in the treatment of hypertension Commercially available in tablets containing 65 and 200 mg and as a 4% elixir Currently there is general agreement with the previous statement that experiences with the drug have been most disappointing and under no circumstances would seem sufficiently promising to hazard the toxic symptoms that apparently occur in one patient in 6 and which include weakne s fatigue muscle pains aphasia confusion mania delirium, collapse coma and death. (p 3896)

Tolserol

A synthetic reducing abnormal neuromuscular mechanism originating in mid brain, brain stem or cord lessening exaggerated reflexes and allaying spasticity Chemically tolserol is 3-ortho-toloxy 1 2 propanediol It is marketed in England as myanesin In America tolserol is commercially available in tablets containing 250 mg and as an elixir compounded so that 1 cc = 100 mg (Squibb) The suggested doses are 4 to 7 tablets taken 3 times daily or 6 to 10 tea poonfuls of elixir 3 times daily Except for some drowsiness untoward side effects have not been ob erved In therapeutic do es tol erol r lieves involuntary movements rigidity spa ticity and tremor It has been employed in tetanus poliomyelitis parkinsonism, hemiplegia cerebral palsy multiple sclerosis and in choreiform and athetotic disturbances Lissephen (Mephenesin) Abbott is identical with tolserol

Trihexyphenidyl

See artane above

MUSCLE RELAXANTS *(Continued)*

Tubocurarine

See chondrodendron tomentosum

Veratrum Viride

Once widely employed as a specific in the reduction of hypertension then discarded as ineffectual and toxic veratrum viride is currently being revived for symptomatic management of hypertension The commercially available preparation Vertavis (Irwin Neisler) has been standardized by the Craw unit based on the amount of reference standard veratrum viride necessary to cause cardiac arrest in daphnia magna the test animal Tablets are available containing 5 or 10 Craw units Using 1 to 2 tablets orally a hypotensive effect occurs within one to two hours with a maximum in four to six hours and disappearance of effect in approximately fourteen hours Laboratory studies reveal that cardiac output is moderately increased and there is an associated reduction in pulmonary arterial pressure

MUSHROOM POISONING

General Principles of Diagnosis and Therapy

1 Mushroom poisoning is due to ingestion of the alkaloid muscarine derived from Amanita phalloides (toadstool) and Amanita muscaria (fly mushroom) With the latter profuse perspiration salivation and lacrimation occur early followed by gastro intestinal symptoms of lesser severity than with toadstool poisoning

2 Mushroom poisoning is heralded by acute abdominal pain vomiting and diarrhea Soon blood is observed in stools and vomitus shortly followed by extreme prostration and generalized weakness Symptoms may persist for two hours or six days followed by complete recovery or death from acute nephritis hepatitis circulatory failure or coma

3 Therapeutic efforts are limited to gastric lavage with normal saline followed by introduction of 2 ounces (60 cc) of 50% magnesium sulfate through the stomach tube The pharmacological antidote for muscarine is atropine sulfate injecting 0 6 to 1 5 mg every four hours

MUSSEL (SHELLFISH) POISONING

General Principles of Diagnosis and Therapy

1 At times ingestion of mussels produces poisoning due to the presence of large numbers of small dino flagellates

2 Soon after the meal patients note tingling and numbness or prickling around the lips followed within ten minutes by paresthesias paralyses ataxia and mental aberrations Only occasionally do patients have gastro intestinal symptoms such as vomiting and pain Death may occur quickly through respiratory failure but if the patient survives twelve hours the prognosis is excellent

3 Therapeutic efforts are limited to evacuation of the gastro intestinal tract by lavage or emetics and purging with a saline laxative

4 Boiling mussels for thirty minutes with 1 ounce of bicarbonate of soda to each quart of water prevents shell food poisoning

MYASTHENIA GRAVIS

Principles of Diagnosis and Therapy

1 Myasthenia gravis is characterized by undue fatigue of voluntary muscles after exercise restitution to normal after a short rest absence of muscular atrophy mild symptoms before noon time as compared with afternoon and evening variable clinical course normal neuro logical examination and symptoms which most frequently consist of ptosis strabismus and diplopia (p 2886)

2 The specific diagnosis is manifest when intramuscular injection of 1 5 mg of neostigmine methylsulfate gives immediate relief and when manifestations are worsened when quinine is prescribed (Table 152 p 2887)

3 The probable pathogenesis of myasthenia gravis is imbalance in the acetylcholine cholinestera e reaction so that acetylcholine is pre vented from exerting its normal effect

4 In mild instances myasthenia gravis is controlled with oral or intramuscular administration of neostigmine

5 In cases of greater severity and in those who fail to obtain com plete relief from neostigmine tetra ethylpyrophosphate (TEPP) may be given orally A 1% solution is prepared in anhydrous propylene glycol and placed in a 20 cc dark glass vial that is tightly capped and waxed The usual therapeutic dose of this anticholinesterase substance is 13 to 17 mg per day in 2 or 3 divided do es

6 Anticholinestera e substances given therapeutically in myasthenia gravis may produce toxic manifestations including muscle fascicula tion spasm of accommodation miosis abdominal cramps diarrhea lacrimation perspiration salivation nausea vomiting restlessness and bradycardia Each of these is relieved by 1 mg (1/60 grain) atropine the pharmacologic antidote

7 When available cortisone and ACTH merit trial Suggestively favorable results have been obtained in a few reported instances

8 With failure of medical treatment look for evidences of thymic enlargement and consider thymectomy Of eight patients subjected to this procedure two were considerably improved four moderately improved one slightly improved and one patient died Of the total of 129 patients reported in the literature 52 per cent seemed to have done well

MYCOSES

[See Fungus Infections]

MYELOMA, MULTIPLE

[See Blood and Blood forming Organs Neoplasms of]

NEOPLASM

The problem of malignancy in neoplasms is the most formidable challenge that currently confronts medical science The urgent need for solution is best indicated by statistical surveys which estimate that there are approximately 800 000 cancer sufferers at any given time in the United States with 185 000 annual deaths

Historically the status of the cancer problem is comparable to that of infectious disease before the time of Pasteur when contagion was attributed to humours or vapours and when the practitioner contributed so little to the survival of his patient that there developed a school of therapeutic nihilists including such great figures as Virchow the pathologist Technologically however the picture is brighter particularly since the forces of medicine and its allied sciences have been mobilized to fight on a common front using weapons of the potential of radioactivity and products of atomic fission

Etiology

Until the cause or causes of malignancy are discovered the development of specific diagnostic tests and curative therapeutic measures appears unlikely Currently the problem of etiology in cancer is confused not by lack of knowledge of carcinogens but by the numbers and varieties of potential causes In the study of cancer investigation has disclosed a gamut of etiologic agents and influences including energy agents such as x rays radioactive substances ultraviolet rays and heat more than 300 chemical compounds viruses parasites (which may be vectors for viruses) endocrine and dietary manipulations and multiple genetic factors (Scheele Bulletin of the New York Academy of Medicine November 1949 p 676)

Early Signs of Cancer

The seasoned general practitioner knows to his dismay and chagrin that the malignant neoplasm is insidious for a considerable span of time Except in those instances in which the lesion is visible to the naked eye (skin or mucous surfaces) accessible to x ray examination (pleura and lungs) or readily palpable by the examining finger (breast and prostate and male and female genitals) the diagnosis of malignancy usually is delayed until advent of complications

For the most part the so-called early signs of malignancy are not caused by the growth itself but by superimposed ulceration infiltration hemorrhage mechanical pressure or obstruction or by development of constitutional disturbances (loss of weight and strength or anemia) or detection of metastases Symptomatic malignancy to which attention is drawn by its complications rather than its intrinsic characteristics is already more than considerably advanced and in consequence less amenable to radical and potentially curative therapy More than any other factor delay in diagnosis is responsible for the fact that only 20 per cent of persons with malignancy are salvaged for five years

'Cancer Detection by the General Practitioner

It is our opinion and in accordance with our experience that cancer detection in the asymptomatic phase of malignancy is best and most unobtrusively accomplished by supplementing routine history and physical examination by a battery of tests most of which are within the scope of the compleat practitioner and his office laboratory The remainder may be referred without fear inspiring comment to the consulting serologist histopathologist roentgenologist surgeon or indicated specialist

Routine History and Physical Survey

The necessity for obtaining a complete history on every new patient, at the initial examination cannot be too often repeated (p 3469) Nor can the admonition to perform a complete physical examination (p 3476) following recital of the history be stressed too often and with too great emphasis

For many years it has been our custom to re-check the history and particularly the 'Pattern of the Way of Life (p 3472) and re assess the physical status of each patient whenever the opportunity arose since only a limited portion of the population realizes the importance of annual and preferably semi annual personal surveys

Health examinations are naturally not limited by the seasoned practitioner to cancer detection alone since asymptomatic phases of many other disturbances notably metabolic and circulatory simultaneously may be brought to light Nevertheless a principal object of the physical survey is that of cancer detection in the asymptomatic phase of malignancy For accomplishment of this purpose the details tabulated on p 4428 merit thoughtful consideration The left hand column of this 'blueprint lists structures under scrutiny with references to normal characteristics and methods for determination of these qualities the right hand column refers to Tables of Differential Diagnosis based on deviations from the norm

CANCER DETECTION

The Practitioner s Physical Survey in the Asymptomatic Phase of Malignancy

Anatomical Structure or Zone	Differential Diagnosis of Objective Findings
Weight (p 3481)	Loss of weight (p 700)
Skin (p 3498)	Nodules cysts and tumors (p 3210)
	Fissures cracks clefts rhagades and ulcers (p 3218)
	Dermatoses of the aged (p 3214)
Cranium (p 3503)	Disturbances of the head in adults (p 3504)
Face (p 3508)	Dermatoses of face (p 3266)
Nose (p 3588)	Dermatoses of nose (p 2110)
	Internal abnormalities of nose (p 3590)
Lips (p 3595)	Disturbances of lips (p 1685)
Mouth (p 3595)	Enanthems involving oral and buccal surfaces (p 1668)
	Disturbances of tongue (p 1687)
	Disturbances of gums (p 1701)
	Disturbances of jaw (p 1705)
	Oral pharyngeal cysts (Table 120 p 1714)
	Disturbances of palate (p 1716)
	Visible abnormalities of throat (p 3600)
Larynx (p 3604)	Abnormalities of larynx observed by endoscopy (p 3606)
Neck (p 3509)	Abnormalities of neck (p 3510)
	Cervical lymphadenopathy (p 3518)
	Swellings and tumors of neck (p 3514)
Trachea (p 3512)	Disturbances of trachea deviation and compression (p 3512)
Thyroid (p 3513)	Swellings and tumors of neck (p 3514)
Parathyroids (p 3515)	Swellings and tumors of neck (p 3514)
Carotid body (p 3515)	Swellings and tumors of neck (p 3514)
Salivary glands (p 3516)	Disturbances of salivary glands (p 3517)
Cervical lymph nodes (p 3519)	Cervical lymphadenopathy (p 3518)
Thorax (p 3522)	Visible abnormalities of chest wall (p 3523)
	Clinical disturbances of breast and nipples (p 2578)
	Axillary lymphadenopathy (p 3526)
	Abnormal movements and pulsations of thoracic cage (p 3528)
	Abnormalities of chest wall noted on palpation (p 3534)
	Abnormalities noted by percussion of chest wall (p 3538)
	Abnormalities noted by auscultation of chest wall (p 3542)
Abdominal wall and cavity (p 3552)	Disturbances of abdominal wall (p 3556)
	Generalized abdominal swellings and tumors (p 1750)
	Swellings and tumors of right upper quadrant (p 1957)
	Swellings and tumors of left upper quadrant (p 1849)
	Swellings and tumors of right lower quadrant (p 1886)
	Swellings and tumors of left lower quadrant (p 1870)
	Swellings and tumors of epigastrium (p 1814)
	Swellings and tumors of hypogastrium (p 2621)
	Enlargements of liver (p 1973)
	Enlargement of kidney (p 2230)
	Splenomegaly (p 1129)
Trunk bony pelvis and extremities (p 3569)	Swellings of back (p 2822)
	Disturbances of ossification (p 2798)
	Monarthralgia (p 2803)
	Increased radiotranslucency of bone (decalcification) (p 2806)
	Painless swellings and deformities involving hips thighs calves and legs (p 2826)
	Swellings of bone (p 2844)
	Painless swellings and deformities of shoulders and upper extremities (p 2954)
	Inguinal swellings and tumors (p 3092)
	Inguinal lymphadenopathy (p 3092)

CANCER DETECTION (*Continued*)

The Practitioner's Physical Survey in the Asymptomatic Phase of Malignancy

Anatomical Structure or Zone	Differential Diagnosis of Objective Findings
Male perineum and genitals (p 3634)	Dermatoses of genitals and perineum (p 3274)
	Swellings and tumors of scrotum and its contents (p 2441)
	Malignancies of testes (p 2444)
	Disturbances of penis (p 2453)
	Rectal examination of anal orifice and prostate (p 3639)
Female pelvis perineum and genitals (p 3641)	Dermatoses of genitals and perineum (p 290)
	Swellings and tumors of hypogastrium (p 2621)
	Inguinal swellings and tumors (p 3092)
	Disturbances of perineum vulva and vagina (p 2548)
	Swellings and tumors of right lower quadrant (p 1886)
	Swellings and tumors of left lower quadrant (p 1870)
	Inspection with bivalve speculum (Fig 1067 p 3647)
	Inspection of cervix of uterus (p 3647)
	Surface biopsy of cervix by method of Ayer (p 4430)
	Bimanual examination of internal genitals (Fig 1068 p 3648)

Cancer Detection in the Office Laboratory

Examinations conducted in the office laboratory are of little value in the detection of asymptomatic malignancy For the most part abnormalities of urine stool and blood reveal deviations due to complications The single exception is the Bolen test which at best is suggestive rather than oracular In our hands it yields many false positive readings

The Practitioner's Laboratory Survey for Cancer Detection in the Asymptomatic Phase

Specimen	Examination	Diagnostic Suggestion
Urine	Bence Jones proteinuria (p 3673)	Multiple myeloma (p 1035)
	Glycosuria (p 3673)	Malignancy of pancreas (p 1943) or anterior pituitary (p 1175)
	Hematuria (p 3683)	Tumors of kidney (p 2326) ureter (p 2326) and bladder (p 2322)
Stool	Occult blood (p 3728)	Melena and tarry stools (p 1843)
Blood	Red cell count (p 3698)	Anemias (p 1058)
		Polycythemia (p 1092)
	White cell count (p 3698)	Leukocytosis (p 1097)
		Lymphocytosis (p 1098)
		Monocytosis (p 1099)
	Bolen test	
	Erythrocyte sedimentation rate (p 3707)	Increased in many miscellaneous disturbances

Technic

1 Clean two glass slides with alcohol Wipe dry
2 Clean fingertip with alcohol Wipe dry Puncture with Hagedorn needle
3 Hold the cleaned glass slides horizontal to the finger With a light touch pick up three separate drops of blood on the back of each slide
4 When blood has thoroughly dried examine pattern under microscope
5 The normal pattern (which can be observed by obtaining specimens from members of the office staff) is compact There are no vacant spaces and red cells are discrete
6 The cancer pattern shows a sludging of cells disappearance of fibrin network and large open lakes of plasma To become familiar with the cancer pattern obtain blood from known carcinomatous individuals and compare with drops obtained from normal controls

by simpler staining methods (such as Wright) Papanicolaou technic reveals more clearly nuclear anisocytosis anisonucleosis hyperchromatism fragmentation abnormal and bizarre forms conspicuousness and mitoses

Greater skill and experience are required for cytodiagnosis than for *any other pathologic technic The practitioner must insist that the* report be rendered by one who is specially trained If there is reasonable doubt as to interpretation end slides for another opinion since the gravity of the situation is sufficiently great to demand all possible protection against errors of false negative or false positive

The Papanicolaou method is not oracular It must not be used to the exclusion of curettage or biopsies if these procedures are possible Whenever feasible check the Papanicolaou slide by histologic sections particularly before performance of a major and irreversible procedure such as gastrectomy hysterectomy or pneumonectomy

Marrow Biopsy

Bone marrow is most easily obtained by sternal puncture (p 1042) best performed by the hematologist so that slides may be prepared instantly after removal of the specimen

Surgical Biopsy

For surgical biopsy remove a lymph node or a generous section of the tumor ma s itself Unless absolutely essential as in punch biopsies of the liver avoid methods of diagnostic aspiration Blind procedures do not provide sati factory specimens for the highly important work of the histopathologist If malignancy is su pected the gravity of the lesion requires that no effort be spared to give the specialist every opportunity to render a satisfactory report With histologic specimens this can be done only by providing tissue sufficiently large for careful handling which has not been macerated in its removal

Electrogastrography

The electrogastrogram currently in its experimental phase provides a trace that resembles the electrocardiogram In the hands of its innovators it is the most delicate method for the diagnosis of gastric malignancy and gives positive findings when all other investigations are still unrevealing The technic of electrogastrography has been modified and adapted by Langman for use in the diagnosis of malignancy of the cervix However the accessibility of cervical tissue to surface or exfoliative cytology renders the Langman trace of less value than the electrogastrogram

SPECIALIZED PROCEDURES FOR THE DIAGNOSIS OF MALIGNANCY

Serodiagnosis

Send 15 or 20 cc of clotted blood to clinical pathologist for Black (methylene blue) Huggins or West Hilliard reactions

Exact figures for the evaluation of the Huggins test are not available but it is

Specialized Diagnostic Procedures in Asymptomatic and Symptomatic Malignancy

Without alarming the patient the practitioner obtains specimens for specialized diagnostic procedures to aid in the diagnosis of asymptomatic malignancy Withdrawal of 15 to 20 cc of clotted blood is all that is required for the trained clinical pathologist or serologist to set up Huggins and Black tests whose implications may be told to the patient after results have been obtained After withdrawal of blood, again without comment material for surface biopsy of the uterine cervix is obtained during vaginoscopy

In symptomatic phases of malignancy additional procedures are required These include simple and contrast roentgenography blood chemical determinations aspiration of bone marrow removal of tissue for biopsy, surgical exploration electro-diagnosis, and the use of radioactive tracers in special institutions equipped for these refinements

Surface and Exfoliative Biopsies (Ayer Papanicolaou)

To obtain material for surface biopsy (Ayer) or exfoliative cytology (Papanicolaou) thoroughly dry mucosa and make a cervical smear using a fine bulb syringe or a cotton applicator Avoid wetting or lubricating vaginal canal since water and oil distort cells and interfere with diagnostic acumen

Spread material uniformly on a clean glass slide Dry in air and fix in equal parts of ether and 95% alcohol before sending to pathologist

Sponge Biopsy (Gladstone)

For sponge biopsy, obtain special set manufactured by Upjohn Company Obtain clear visualization of lesion whether on skin uterine cervix mouth rectum or recto sigmoid Wipe with several cotton sponges before rubbing diagnostic Gelfoam sponge over base of ulcer

For sponge biopsy of cervix first use larger flat piece over lips of cervix and external os Then insert second narrower piece into cervical canal for a distance of 0 5 to 1 cm Place sponge or sponges in a small bottle of 10% formalin (provided with set) and send to pathologist

Button Biopsy

For button biopsy centrifuge specimen and decant supernatant fluid Treat button of sediment as a histologic section or spread on slide and stain by method of Papanicolaou

Cytodiagnosis of Malignancy

Earliest changes in malignancy are reflected in the nuclear structure of superficial or exfoliated cells To delineate these histologic variants with greatest clarity Papanicolaou has devised a complicated staining reaction which renders cytoplasm transparent and brings out nuclear detail in finest intricacy

While the same changes to a lesser degree may be demonstrated

With the exceptions of androgen in breast malignancy estrogen in prostatic malignancy and a trial of teropterin in miscellaneous metastatic cancers available anticarcinogens are disappointing in their effectiveness or excessively toxic for use by the general practitioner Notable among ineffectual products is the Russian antireticular cytotoxic serum Among hazardous preparations are bacterial filtrates which nevertheless on occasions have produced remarkable clinical improvement at the price of severe febrile and local reactions

Under pressure the isolated practitioner with a well equipped office laboratory also may use aminopterin and urethane in the treatment of leukemia Additionally injections of stilbamidine may be tried as a desperation resort in the rarely encountered multiple myeloma provided that risks are understood by some responsible member of the family

ANTICARCINOGENIC THERAPY AVAILABLE TO THE PRACTITIONER

ACS (Anti Reticular Cytotoxic Serum)

Unpromising report in a variety of neoplasms negative results in mycosis fungoides no evidence of a fundamental effect on the neoplasm in 22 cases of Hodgkin s disease (Gellhorn and Jones Am J Med 6 195 1949)

Aminopterin (4-amino-pteroyl glutamic acid)

A folic acid antagonist used in the treatment of *acute leukemia* Daily subcutaneous or intramuscular injections of 0 5 to 1 0 mg produce remissions in approximately 50 per cent of children and 30 per cent of adults Continue therapy until remission unless toxic manifestations appear sooner (severe dermatitis ulceration of intestinal epithelium with hemorrhage pancytopenia with anemia leukopenia thrombocytopenia and alopecia) Also merits trial in Hodgkin s disease lymphosarcomas and neuroblastomas

Androgen

Intramuscular injections of 100 mg three times weekly for eight to ten weeks in metastatic breast malignancy provide relief of pain and subjective well being Do not use to exclusion of surgery and irradiation Preferably employed in conjunction with the latter two or after they have been fully utilized Consider use in prophylaxis before metastases appear (p 4192)

Anterior Pituitary Corticotropic Hormone (ACTH)

Anterior pituitary corticotropic hormone when available may produce remissions in leukemias Hodgkin s disease and malignant lymphomas (p 4146)

Bacterial Filtrates

Mixed toxins of S erysipelas and B prodigiosus (Coley) and filtrates of S marcescens (Brues and Shear) show occasional palliation but with marked systemic reactions often associated with hemorrhage and necrosis of neoplasms S cruzi endotoxins (KR) though reported to produce a favorable response by the Russians (Klyueva) have been disappointing in the hands of American investigators Application in human neoplastic disease for the present is hazardous and of doubtful efficacy (Gellhorn and Jones)

Diopterin

Pteroyl Glutamic acid See Teropterin

Ethyl Carbamate

See Urethane

probable that negative results are over 95% accurate and positive results about 80% accurate False positives occur in patients with pulmonary tuber culosis chronic nephritis benign prostatic hypertrophy lobar pneumonia and pregnancy There is a possibility that the test is less reliable in older age groups

Cytodiagnosis

Surface biopsy of normal cervix (Ayer)
Exfoliative biopsy using material from ulcerated cervix, gastric contents sputum pleural fluid peritoneal fluid urine or scrapings obtained by sig moidoscopy (Papanicolaou)
Sponge biopsy (Gladstone) button biopsy using sediment of centrifuged specimen such as pleural or ascitic fluid or urine

X ray

Simple roentgenograms for chest, skull and other bones (Table 196 p 3741)
Contrast roentgenography for digestive urinary respiratory or nervous sys tens or peri renal tissues (Table 197 p 3742)

Blood chemistry (p 3712)

Hyperglycemia in hyperpituitarism and adrenal cortical chromaffinomas (p 773) *Hypoglycemia* in adrenal cortical deficiency hypopituitarism and hyperinsulinism due to malignancy of the pancreas (p 734)
Hypercalcemia in adenomas of parathyroid and of basophile tissue of anterior pituitary (p 723) *Elevated acid phosphatase* in prostatic carcinomatosis (p 728)
Hyponatremia in adrenal cortical deficiency (p 729) *Hypernatremia* in basophile adenomas of anterior pituitary and neoplasms of adrenal cortex (p 730)
Hypopotassemia in adrenocortical hyperfunctioning tumors and hyperpitui tari m (p 731)
Hyperglobulinemia and *hyperproteinemia* in multiple myeloma leukemia and lymphosarcoma (p 735)

Marrow aspiration (p 1042)

For diagnosis of leukemia polycythemia multiple myeloma Hodgkin s disease and metastatic carcinomatosis (Table 68 p 1043)

Surgery

For biopsy or exploration

Electrodiagnosis

With special electrodes obtain graphs from stomach (Goodman) or uterine cervix (Langman)

Radioactive tracers

Uptake of P^{32} for tumors of breast or testes Also use during surgery for brain tumors
Uptake of I^{131} *(diiodofluorescein)* for detection of thyroid tumors and of brain tumors before surgery Refer to institutions provided with radioactive material by the Atomic Energy Commis ion And equipped with special apparatus such as Geiger counters etc

Anticarcinogenic Therapy by the Practitioner

Effective anticarcinogenic therapy requires radical surgery and/or powerful radiotherapy Each of these modalities is beyond the scope of the general practitioner who must necessarily use instrumentalities whose technical demands are less exacting

Anti Carcinogenic Therapy by the Specialist

Radical surgery and irradiation are the principal agents for attempted radical cure of malignancy Under special circumstances the two therapeutic agencies are combined using irradiation preoperatively and/or postoperatively

Roentgen therapy may be made less toxic to the host and more destructive to the malignancy by simultaneous administration of aureomycin Additionally surgical and/or roentgen therapy may be fortified by concurrent hormone therapy including castration in breast and prostate malignancies and injections of gonadal hormone of the opposite sex following castration Thus the female receives androgen for symptomatic relief and anticarcinogenesis in malignancies of the breast and the male estrogen for similar purpose

In leukemia and malignant lymphomas including Hodgkin s disease other special tools are available to the expert working in institutions provided with special equipment Nitrogen mustard P^{32} Na 24 I^{131} and Au 198 are under experimental investigation in specially equipped laboratories

ANTI-CARCINOGENIC MEASURES EMPLOYED BY CONSULTANT SPECIALISTS

Anterior Pituitary Corticotropic Hormone (ACTH)

Use by special allocation in the treatment of leukemias Hodgkin s disease and other malignant lymphomas (p 4146)

Au 198

Radioactive gold prepared by license of the Atomic Energy Commission Inject directly into malignant tumor masses in doses of 4 mg Employed in Hodgkin s disease lymphosarcoma chronic lymphatic leukemia and squamous cell carcinomas of nose and eyelids

Castration

Of female in breast malignancy Of male in prostatic malignancy Simultaneously give androgen injections to the female and estrogen injections to the male

Cortisone (adrenocortical extract)

Use under special allocation in the manner of ACTH (p 4145)

Excision

Surgical treatment of choice particularly in treatment of asymptomatic malignancy

I^{131}

Radioactive iodine prepared by license of the Atomic Energy Commission For treatment of thyroid malignancy and its metastases after total thyroidectomy

Irradiation

Using x ray or radium procedure of choice pre operatively postoperatively in association with surgery and in the surgically inoperative malignancies Use aureomycin concurrently to minimize radiation sickness and permit use of larger doses

Isotopes

See Au 198 I^{131} and P^{32}

ANTICARCINOGENIC THERAPY AVAILABLE TO THE PRACTITIONER (Continued)

Estrogen

Use orally or by intramuscular injection in carcinoma of the prostate preferably in conjunction with castration Constitutes the single most outstanding practical contribution to the chemotherapy of malignancy retards the neoplastic growth of prostatic epithelium (Gellhorn and Jones) Use also in post menopausal females with profuse nonosseous carcinomatoses secondary to breast malignancy (p 4325)

Folic acid conjugates and analogs

See Teropterin.

Folic acid antagonists

See Aminopterin

Stilbamidine

Suggested for carcinogenic action in multiple myeloma Inject 150 mg intramuscularly with 2% procaine to total 3 to 6 gm (20 to 30 daily injections) Toxic reactions frequent fundamental lesions not significantly altered To be used only as a last therapeutic resort (p 4222)

Teropterin

Folic acid conjugates and analogs produce regression in a significant number of instances of mouse sarcoma 180 Preparation available as teropterin (Lederle) in ampuls and vials containing 10 mg to the cc Inject intramuscularly once daily for the first week in doses of 1 cc and twice daily for three or four weeks Teropterin possesses no toxicity in the recommended doses It must not be used to the exclusion of surgery and irradiation

The Council on Pharmacy and Chemistry of the A M A 1948 reviewing the treatment of 275 patients noted only that relief and subjective improvement was reported in 50% of patients Despite negative reports in mass statistics we have observed three remarkable instances of survival seemingly due to teropterin It is our opinion that a course of teropterin merits trial by the practitioner particularly since the preparation has no toxicity and if it accomplishes nothing else it gives the practitioner something tangible to do when he visits his patients with metastatic malignancy Additionally it satisfies the demanding family which insists that something be done

Urethane (Ethyl Ester of Carbamic Acid)

Urethane is commercially available in pint and gallon bottles (Abbott) Each 30 cc contains 4 gm of the drug Oral doses of 4 cc twice daily to total 1 gram reduce leukocyte counts in chronic myelogenous leukemias Toxic effects include anemia leukopenia thrombocytopenia ecchymose hematuria and pulmonary edema If there is an absence of toxic symptoms and a favorable therapeutic response doses may be increased by increments of 4 cc to maximum daily dose of 44 cc (4 5 gm) Under favorable conditions with reduction of total leukocyte count to 10 000 or 20 000 WBC and in the absence of toxic symptoms maintenance doses approximating 1 gm daily (8 cc of commercially available preparation) may suffice Urethane is less useful but merits trial in chronic lymphatic leukemia A satisfactory therapeutic agent in producing temporary remission in chronic lymphatic and myelogenous leukemia (Gellhorn and Jones) May be an additional useful weapon against prostatic carcinoma (Huggins) though the use of the drug is potentially hazardous since it can produce marked depression of bone marrow functions (Webster)

INOPERABLE MALIGNANCY

Practical Management

1 For the female with metastatic breast malignancy or an ovarian neoplasm advise roentgen or surgical castration followed by injections of androgen

2 For the male with prostatic or testicular malignancy advise surgical or roentgen castration with injections of estrogen

3 In all patients try the effects of teropterin Give 1 cc intramuscularly or intravenously daily for three weeks Then suggest a treatment holiday with the understanding that therapy will be resumed In this way if nothing else is accomplished the patient receives psychotherapy and does not feel completely abandoned to fate

4 Give sedatives during the day to those who are confined to the house or bedridden Prescribe a hypnotic each night

5 For pain unrelieved by measures above indicated supplement with an analgesic antipyretic such as acetylsalicylic acid in doses of 0 3 to 0 6 gm several times daily

6 Suggest free use of the patient s favorite alcoholic beverage in order to save opiates for more serious discomfort

7 When driven to the opiates start with oral preparations such as methadone or metopon so that the patient does not have to be given drug by hypodermic Try to use smallest possible doses such as 2 5 mg two or three times daily Increase to 10 mg three or four times daily if necessary before proceeding to next preparation

8 When oral opiate no longer gives comfort pass on to hypodermic use of demerol since this has minimum side effects on bladder and rectum Begin with doses as small as 50 mg if possible but progress to 200 mg three or four times daily if needed

9 Cautiously try synergism with scopolamine (hyoscine) To opiate add 0 25 to 0 5 mg *in probatory fashion*

10 Finally in desperation substitute dilaudid or morphine itself At this time consider surgical aid additionally

11 In consultation with specialist anesthetist or surgeon discuss operative intervention If pain is localized attempt nerve block sympathectomy or chordotomy However if these measures fail or if pain is widespread and generalized consider lobotomy which is a relatively simple technical procedure in the hands of the expert and which gives amazing results for relief of pain and addiction

For the more concrete management of neoplasms in various structures of the body consult the following

Blood and blood forming organs neoplasms of
Digestive system neoplasms of
Endocrines neoplasms of
Female reproductive system neoplasms of
Male reproductive system neoplasms of
Nervous system neoplasms of
Respiratory system neoplasms of

Nitrogen Mustards

Highly toxic war gase injected intravenously to produce temporary remissions in Hodgkin s disease lymphosarcoma leukemia mycosis fungoides poly cythemia vera and miscellaneous malignant lymphomas Because of toxicity recommended only in surgically inaccessible growths and in patients who have become roentgen re istant (p 4439)

Surgery

Radical removal by excision is procedure of choice May be accompanied by pre-operative or postoperative radiation May be accompanied concurrently by castration particularly in malignancies of breast and prostate and hormone therapy

Palliative Therapy of Inoperable Malignancy

Practitioner and consultant specialist cooperate in an effort to afford palliation to the victim of inoperable malignancy For the most part the problem is relief of pain It is customary to start with least effectual remedies holding in reserve more potent modalities against greater intensity of anguish at a later date

When drugs fail surgery merits consideration starting with the simple injection or nerve block and proceeding to the more complicated sympathectomy chordotomy or lobotomy

PALLIATION TREATMENT FOR PAIN RELIEF IN INOPERABLE MALIGNANCY

Sedatives (p 3836)

For use during day with or without analgesics

Hypnotics (p 3836)

For use at night with or without analgesics

Analgesic Antipyretics (p 3832)

Try non habituating preparations before recourse to opiate and their substitutes

Opiates and Substitutes

Prefer less objectionable synthetics such as methadon (p 4416) metopon (p 4417) and meperidine (isonipecaine demerol) before being driven to dihydromorphinone (dilaudid) or morphine sulfate Try combinations with sedatives hypnotics scopolamine and analgesic-antipyretics

Nerve block

Alcohol injections by specialist, if possible

Sympathectomy

By consulting neurosurgeon

Chordotomy

By consulting surgeon, particularly with spinal cord meta tases

Lobotomy

Of inestimable value in diffuse intractable pain, uncontrolled by opiates and their synthetic substitutes

INOPERABLE MALIGNANCY

Practical Management

1 For the female with metastatic breast malignancy or an ovarian neoplasm advise roentgen or surgical castration followed by injections of androgen

2 For the male with prostatic or testicular malignancy advise surgical or roentgen castration with injections of estrogen

3 In all patients try the effects of teropterin Give 1 cc intramuscularly or intravenously daily for three weeks Then suggest a treatment holiday with the understanding that therapy will be resumed In this way if nothing else is accomplished the patient receives psychotherapy and does not feel completely abandoned to fate

4 Give sedatives during the day to those who are confined to the hou e or bedridden Prescribe a hypnotic each night

5 For pain unrelieved by measures above indicated supplement with an analgesic antipyretic such as acetylsalicylic acid in doses of 0 3 to 0 6 gm several times daily

6 Suggest free use of the patient s favorite alcoholic beverage in order to save opiates for more serious discomfort

7 When driven to the opiates start with oral preparations such as methadone or metopon so that the patient does not have to be given drug by hypodermic Try to use smallest possible doses such as 2 5 mg two or three times daily Increase to 10 mg three or four times daily if necessary before proceeding to next preparation

8 When oral opiate no longer gives comfort pass on to hypodermic use of demerol since this has minimum side effects on bladder and rectum Begin with doses as small as 50 mg if possible but progress to 200 mg three or four times daily if needed

9 Cautiously try synergism with scopolamine (hyoscine) To opiate add 0 25 to 0 5 mg in probatory fashion

10 Finally in desperation substitute dilaudid or morphine itself At this time consider surgical aid additionally

11 In consultation with specialist anesthetist or surgeon discuss operative intervention If pain is localized attempt nerve block sympathectomy or chordotomy However if these measures fail or if pain is widespread and generalized consider lobotomy which is a relatively simple technical procedure in the hands of the expert and which gives amazing results for relief of pain and addiction

For the more concrete management of neoplasms in various structures of the body consult the following

Blood and blood forming organs neoplasms of
Digestive system neoplasms of
Endocrines neoplasms of
Female reproductive system neoplasms of
Male reproductive system neoplasms of
Nervous system neoplasms of
Respiratory system neoplasms of

Skeletal system neoplasms of
Tegumentary system neoplasms of
Urinary system neoplasms of

NERVOUS SYSTEM NEOPLASMS OF

Neoplasms of the central nervous system are problems for the specialist In their management the practitioner functions for early diagnosis and rapid reference

The diagnosis of neoplasms of the central nervous system is made difficult through protection of brain and cord by bony structures Inspection and palpation yield no information The early signs for the most part are inferential resulting from increased intracranial or intraspinal pressures and from chance involvements of cranial or spinal nerves

Fortunately in the practitioner s experience primary malignancies of the central nervous system are infrequently encountered Unhappily however *metastases (particularly from cancers of breast prostate* and digestive tract) are seen with great frequency

BRAIN TUMORS

Practical Management

1 Note manifestations of increased intracranial pressure (p 1421) or of localized neurologic signs (p 1423)

2 Examine fundus oculi for papilledema or optic atrophy (Fig 269 p 1422)

3 Get blood for serodiagnosis of malignancy (p 4431)

4 X ray skull Note deformities of sella turcica (Fig 248 p 1177) abnormal calcifications (Fig 268 p 1421) or unusual hyperostoses (Fig 270 p 1423)

5 Obtain an electro encephalogram (Fig 273 p 1427)

6 Refer to consultant neurologist or neurosurgeon for re assessment of neurologic status Under his direction perform lumbar puncture and make manometric readings Send spinal fluid to clinical pathologist for cell count protein estimation determination of sugar content colloidal gold curve search for tubercle bacilli serologic tests for syphilis and guinea pig inoculation

7 Discuss the possibility of obtaining additional information from ventriculography (Fig 71 p 1424) or encephalography (Fig 272 p 1425)

8 If facilities are available consider injection of radioactive isotope for tracer diagnosis

9 Discuss exploratory craniotomy

SPINAL CORD TUMORS

Practical Management

1 Look for clinical evidences of cord pressure (Fig 274 p 1431 and p 1430) and for localized neurologic signs (p 1423)

2 Get anteroposterior lateral and lateral oblique radiographs of vertebral column

3 Obtain blood for serodiagnosis of malignancy (p 4431)

4 Perform lumbar puncture Make manometric readings (pp 1434 and 3735)

5 Send spinal fluid to clinical pathologist for cell count protein estimation determination of sugar content colloidal gold curve search for tubercle bacilli serologic tests for syphilis and guinea pig inoculation

6 Consult specialist neurologist or neurosurgeon for re assessment of neurologic status Discuss contrast laminography through introduction of iodized oil

7 If facilities are available consider injection of radioactive isotopes for tracer diagnosis

8 Discuss exploratory laminectomy

NEWCASTLE VIRUS DISEASE (HUMAN)

General Principles of Diagnosis and Therapy

1 Avian pseudo plague or pneumoencephalitis (Newcastle virus disease) is commonly observed among domestic fowl It is unusual for the diagnosis of this infection to be made in the human being

2 Gough (Ohio State Med J 45 25 1949) observed ten patients who developed the syndrome after eating chicken Clinical manifestations included nausea vomiting fever malaise anorexia abdominal pain lumbar pain and headache The diagnosis was confirmed by virus neutralization tests

3 Epidemiologic studies suggest that the incubation period of Newcastle virus disease varied from two one half to five or more days The uspected chickens were said to have been thoroughly cooked

4 It is suggested that warnings be issued to those who kill and dress their own poultry to reject fowl afflicted with avian pseudoplague

5 A trial of treatment with aureomycin or chloramphenicol merits consideration

NITROGEN MUSTARD

Nitrogen mustard is employed by special investigators in the treatment of the leukemias Hodgkin s disease and other malignant lymphomas In the majority of present investigations the bis form of nitrogen

mustard is preferred in doses of 0 1 mg per kilogram of body weight injected intravenously

Technic Goldman and associates (Arch Int Med 82 125 1948) inject nitrogen mustard through an intravenous infusion of 1000 cc of isotonic sodium chloride solution After the infusion is started a solution of nitrogen mustard crystals is made by introducing 10 cc of isotonic sodium chloride into a bottle containing 10 mg of the drug The required amount of solution is then withdrawn in the dose of 1 cc for each 10 kilograms (22 lbs) of body weight This amount is injected immediately into the rubber tubing of the running sodium chloride infusion Immediate injection is essential since nitrogen mustard is hydrolyzed and becomes ineffective after a few moments

Available Preparation

Mechlorethamine Hydrochloride (methyl bis [β chloroethyl] amine hydrochloride) is available in cartons of four rubber stoppered vials each vial containing 10 mg of the drug triturated with sodium chloride *q s ad* 100 mg (Merck)

Therapeutics

Nitrogen mustards exert a powerful cytotoxic reaction resembling in some respects the effects of roentgen irradiation Most susceptible to the cytotoxic action of nitrogen mustards are formed elements of the blood and gastro intestinal mucosa Initially this is manifest by reduction in the numbers of leukocytes neutrophilic granulocytes and lymphocytes Later erythrocytes and thrombocytes are effected

RESULTS OF NITROGEN MUSTARD THERAPY

Diagnosis	Total No of Patients Treated	Per Cent Improved
Hodgkin s disease	107	92
Lymphosarcoma including reticulum cell sarcoma	34	52
Acute leukemia	14	36
Myelogenous leukemia	19	42
Lymphatic leukemia	16	75
Mycosis fungoides	4	75
Polycythemia vera	6	100
Miscellaneou (teratoma of testis chronic reticuloendotheliosis giant follicle lymphoma sympathoblastoma multiple myeloma etc)	18	80

Adapted from Goldman Arch Int Med 82 125 1948

In the treatment of Hodgkin s disease where nitrogen mustard is most effectual reduction in formed elements of blood is associated with therapeutic manifestations of defervescence decrease in glandular enlargement and weight gain Remissions are produced more rapidly than with roentgen irradiation but they are of no longer duration For the most part nitrogen mustard therapy is reserved for those who have become roentgen resistant Following a course of nitrogen mustard

sensitivity to roentgen therapy may be restored Whether alternation of nitrogen mustard and irradiation or combined therapy provides optimum results remains as yet to be determined

Besides Hodgkin s disease nitrogen mustards produce remissions (similar to those effected by roentgen irradiation) in malignant lymphomas lymphosarcoma chronic lymphatic leukemia and polycythemia vera

Toxicity

Nausea and vomiting are universal but transitory There is no reported instance of serious diarrhea The formed elements of the blood are persistently depressed for two to four weeks No fatal infection has been reported in spite of counts as low as 200 leukocytes per cubic millimeter All patients who survive sufficiently long appear to make a satisfactory recovery from drug toxicity No toxic rashes have been observed

ONCHOCERCIASIS

Treat with hetrazan as in filariasis (p 4327)

ORNITHOSIS

(Psittaco is Parrot Fever)

General Principles of Diagnosis and Therapy

1 Ornithosis is a specific infection produced by an organism midway between rickettsias and viruses (p 473)

2 The etiologic agent is a coccoid elementary body tinctorially demonstrable with basic dyes and readily seen under the ordinary microscope It contains intracellular inclusion bodies and is held back partially or completely by ordinary filters It is readily propagated in the yolk sac and embryonated hens egg and in tissue cultures

3 The organism of ornithosis is closely related to a large group of similar pathogenic microbes including those of lymphogranuloma venereum murine and feline pneumonitis meningeal pneumonitis spontaneous mouse pneumonitis Australian mouse pneumonitis human virus pneumonitis Illinois virus pneumonitis and Louisiana virus pneumonitis

4 In addition to exotic birds the virus of ornithosis is transmitted by domestic animals such as ducks

5 The diagnosis may be established by culture of the invading organism in specially equipped laboratories and by complement fixation tests made one week after recovery

6 The virus or rickettsia of ornithosis responds specifically to penicillin aureomycin and chloramphenicol

Practical Management

1 Isolate patient and inaugurate non specific treatment for infection (pp 67–73)

2 Deposit 300 000 to 600 000 units of procaine penicillin G in aqueous solution or suspension Prepare to maintain antibiotic levels by use of a similar daily dose If the patient cannot be seen daily deposit penicillin in sesame oil with 2% aluminum monostearate (p 4453)

3 In the presence of patient sensitivity or organism resistance substitute aureomycin or chloramphenicol Give either in a loading dose approximating 50 mg per kg of body weight (3 5 gm for the average adult weighing 150 lbs) Administer the priming dose through ingestion of 2 products every few minutes accompanied by small amounts of milk ice cream cream cheese or fruit drink Four hours after the priming dose has been taken start daily maintenance doses using an amount equal to the priming dose divided into 4 equal portions given at 6 hour intervals

4 If patients are severely ill or fail to respond with sufficient rapidity to penicillin or if their general condition is such that speed of recovery is essential supplement penicillin with aureomycin or chloramphenicol using priming and maintenance doses as above

ORTHOXINE HYDROCHLORIDE

Orthoxine hydrochloride is a new sympathomimetic amine

Available Preparations

Orthoxine Hydrochloride Tablets (Upjohn) 100 mg

Pharmacology and Therapeutics

Like isuprel and isonorin orthoxine has a specific bronchodilator effect It is essentially free from vasopressor cardiac and central nervous system effects as manifested by epinephrine and ephedrine

For treatment of mild and moderate paroxysms of asthma order 1 or 2 tablets and repeat in three or four hours For prevention of attacks suggest a 100 mg tablet three or four times daily (p 4270)

OXYQUINOLINES

The oxyquinolines are iodine-containing compounds used as amebacides (p 4182) and trichomonacides (p 4592)

OXYQUINOLINE PRODUCTS

Name	Available Commercial Products	Comments
Chiniofon (Anayodin Quinoxyl) U S P	Chiniofon Tablets (enteric coated) 250 mg (Abbott Premo Endo Winthrop) Anayodin Tablets (enteric coated) 250 mg (Bischoff) Quinoxyl Tablets 250 mg (Burroughs Wellcome)	For treatment of amebiasis giardiasis or balantidiasis give 1 gm three times daily for one or two weeks Repeat after rest of ten days if necessary
Diodoquin N N R	Diodoquin Tablets 210 mg (Searle)	Favored oxyquinoline compound Most effective and least likely to cause treatment diarrhea on the second or third days of administration In amebiasis especially effective against intra intestinal forms Sterilizes cysts especially in asymptomatic carriers
Vioform N N R	Vioform Tablets 250 mg (Ciba) Vioform Vaginal Inserts 250 mg (Ciba) Vioform insufflate 25% (Ciba)	As amebacide give 250 mg four times daily for ten days As trichomonicide insert vaginal tablets or insufflate powder

OXYURIASIS

[Seat Worm Pinworm Infestation]

Principles of Diagnosis and Therapy

1 Oxyuriasis is the most common helminthic infestation observed in the Americas (p 1902)

2 Establish the diagnosis by obtaining an anal specimen using the NIH swab (Fig 437 p 1903) From this ingenious device ova may be recognized microscopically (Fig 433 p 1894)

3 Since oxyuriasis is a familial household infection treat all members of the family simultaneously to prevent constant reinfection

4 Instruct individuals of the manner in which the life cycle of the pinworm is accomplished Egg are transferred from anal region to mouth through errors in personal hygiene Warn patients to wash hands thoroughly after urination enemas and defecation and again before meals Each should anoint anogenital regions thoroughly after stool with 2% ammoniated mercury Finger nails are cut short Toilet seats are scrubbed daily with 1/1000 bichloride of mercury Bed and personal linen are boiled before washing Infants and children mu t wear snug cotton drawers and gloves at night to prevent auto inoculation

Practical Management

1 As anthelmintic of choice use gentian violet in four hour Seal Ins The adult is given 2 tablets each containing 30 mg three times daily one hour before meals for eight days After a rest period of one week the eight day course is repeated

2 As an alternative tabloids of diphenan (p benzylphenylcarbamate) are advised Diphenan is marketed (Burroughs Wellcome) in winter green flavored wafers containing 0 5 gm For the adult order one or two of these three times daily after meals for one week Nightly during treatment and every second night thereafter the patient takes an enema made by dissolving a teaspoonful of bicarbonate of soda in a half pint of warm water After discharging the bicarbonate enema another is taken with one heaping tablespoonful of salt to another half pint of water If possible the saline enema is held for ten minutes

3 At the end of treatment the patient takes a saline laxative of 30 to 45 gm of sodium sulfate

4 More toxic than gentian violet or diphenan is phenothiazine (dibenzo 1 4 thiazone) which may be used in refractory cases Daily doses of 0 25 gm are given four times daily for four to six days Toxic symptoms include nausea vomiting hematuria albuminuria and aplastic anemia

PAMAQUIN NAPHTHOATE N F

Prior to introduction of chlorguanide pamaquin appeared to be the one antimalarial capable of activity against sexual forms or gametocytes of falciparum malaria Despite its toxicity (p 519) it merited employment for the sole purpose of destruction of the silent pool from which the mosquito vector might obtain P falciparum for infection of other patients (p 4294)

The efficacy and relative nontoxicity of chlorguanide relegates the potentially hazardous but once useful pamaquin (plasmochin) to the growing list of obsolete derivatives which the practitioner fortunately has no longer to consider in the treatment of malaria (p 507)

Available Product

Plasmochin Naphthoate N F (Winthrop) Tablets 20 mg

Therapeutics

See p 519

Dosage

Against gametocytes of falciparum 20 mg thrice daily for three days with 1 gm sodium bicarbonate

Toxicity

See p 519

PARA AMINOBENZOIC ACID (PABA)

Introduction of para aminobenzoic acid as an antibiotic agent rep resented another paradox in the treatment of bacterial invasion (p 4219) Para aminobenzoic acid which nullifies the activity of sul fonamides is both rickettsicidal and amebacidal (p 4182)

Available Products

Tablets Sodium PABA 0 5 gm (International Vitamin Co and Wyeth)

Therapeutics

PABA exerts a depressant action on the metabolism of rickettsia and amebas It is of proven value in the treatment of typhus fever Rocky Mountain spotted fever tsutsugamushi fever and other rickettsioses (p 4506) Despite its efficacy it already has been superseded by aureomycin and chloramphenicol in the management of rickettsemias

PABA may prove permanently useful however in the treatment of amebic dysentery (p 4182) and allied infestations such as giardiasis (p 4345) and balantidiasis (p 4254) It is also on trial in the manage ment of rheumatic fever

Dosage

The initial therapeutic dose of PABA is 4 to 6 gm followed by 2 to 3 gm every two hours night and day

Blood levels of 30 to 50 mg per 100 cc of PABA must be obtained and maintained for maximum effects

Toxicity

With levels greater than 50 mg per 100 cc of PABA in the blood there may appear evidences of renal or hepatic irritation These how ever are reversible when the antibiotic is discontinued

PABA is not given in conjunction with sulfa compounds whose anti bacterial effects it nullifies It may be given however with penicillin streptomycin aureomycin or chloramphenicol

PARAGONIMIASIS

[Pulmonary Distomiasis Lung Fluke]

Principles of Diagnosis and Therapy

1 Paragonimiasis is a pulmonary infestation with the lung fluke The diagnosis is established by finding ova or parasites in sputum Fre quently paragonimiasis is associated with pulmonary tuberculosis

2 Paragonimiasis does not respond well to the antimonials but is relieved by courses of emetine (p 529)

PEDICULOSIS

General Principles of Diagnosis and Therapy

1 Pediculosis occurs on head (P capitis Fig 901 p 3183) body (P vestimentorum corporis) or pubis (P pubis crabs Fig 902 p 3183)

2 The diagnosis is established by identification of the causative organism (Fig 903 p 3184) and its ova (nits)

3 Diagnosis and therapy are of more than passing importance since pediculi may be vectors of typhus and relapsing fevers (Table 2 p 42)

4 Delousing is accomplished on a mass scale by use of insecticides particularly those containing DDT (p 4373)

5 For the individual treatment is best conducted with the least toxic preparation For this purpose Kwell represents first choice using this preparation as in scabies (p 4514)

6 Second choices include benzyl benzoate and lotio bornate also used as in the treatment of scabies

7 Obsolete are older pediculocides benzene kero ene and larkspur

8 Too toxic for clinical use are beta naphthol benzoate lethane 384 mercurial preparations rotenone and the proprietary cuprex DDT has proven much less efficacious than the preparations of choice above mentioned

9 In addition to use of pediculocide the patient must be instructed in methods of preventing dissemination and reinfection These include boiling of linen and bed clothes sterilization of toilet seats treatment of other members of the household and other contacts etc

10 Secondary bacterial infection of pediculosis is exceedingly common Pyoderms require local therapy with an antibiotic such as bacitracin or tyrothricin unless there are systemic manifestations under which circumstances deposit penicillin as in other pyogenic infections

PEDICULOCIDES

Preparation	Comment
Benzine	Obsolete inflammable
Beta naphthol benzoate (Merck, Mallinckrodt)	In 3 to 10% ointment Prefer less toxic preparations (p 4447) May cause renal and ocular lesions
Benzyl benzoate U S P (Lilly Merck Mallinckrodt Breon Dorsey Burroughs Wellcome)	Effective in 20 or 25% lotion (p 4446) A safe and effective preparation of choice Avoid contact with eyes
Bornate (Wyeth)	Available lotion is a 5% solution of isobornyl thiocyano acetate Effective and safe pediculocide of choice (p 4447)
Cuprex (Merck)	Effective proprietary copper pediculocide (p 4446) Contains tetrahu acetone copper and liquid paraffin Inflammable May cause porphyrinuria (p 4628)
DDT	Use in 10% strength in talc or pyropyllite Not as effective as other pediculocides
Delphinium	Obsolete
Kerosene	Obsolete inflammable

PEDICULOCIDES (*Continued*)

Preparation	Comment
Kwell (C S C)	A vanishing cream ba e containing 1% hexachlorocy clohexane (p 4447) Effective and safe pediculocide of cho ce
Larkspur	Obsolete
Lethane (p 384)	Use as 15% solution in kerosene Effective but in flammable Not commercially available
Mercury	Use as 3 to 10% ammoniated mercury ointment. Messy and dangerous Obsolete Prefer newer preparations (p 4447)
Rotenone	Too toxic for clinical use (p 4446)

Practical Management

1 After a hot bath rub 25 to 50 gm of Kwell ointment (C S C) into affected area

2 Refrain from bathing or washing for twenty four hours

3 After twenty four hours bathe and don fresh underclothes night clothes and linen

4 Repeat treatment in one week if necessary

5 If lotion bornate (Wyeth) is substituted work 30 to 60 cc into lather at site of infestation After five to ten minutes if irritation is not exces ive comb hair and let skin dry Repeat in a few moments or an hour if necessary

PELLETIERINE TANNATE U S P

Becau e of its toxicity (p 1896) pelletierine has been replaced by oleoresin of aspidium (p 4197) in the treatment of teniasis

If pelletierine is substituted a single oral dose of 250 mg is inter polated in the routine described for aspidium therapy

PENICILLIN

Historical Review The remarkable properties of penicillin were recognized before the first printing of the Integrated Practice of Medicine (1946) The text detailed its source and isolation chemical and physical propertie and methods used for biological standardization (p 106) it listed the then available preparations and discussed their absorption excretion mechanisms of action therapeutics toxicity and indications for use in specific probatory and desperation-antibiotic therapy (p 114)

Enthu ia m for penicillin s a tounding virtues did not obscure many unsolved problems in antibiotic therapy Penicillin was not virucidal or antirickettsial gram negative bacilli were relatively re istant, in the treatment of penicillin sensitive organisms materials were scarce costs were high available preparations were unstable and results were occasionally inconsistent oral administration was unsatisfactory nece sitating parenteral introduction and rapid excretion through kidneys required frequent injec tions by day and night in order to maintain effective levels in blood and tissues

In the brief years that have elapsed since publication of earlier material there has been ample confirmation of all basic facts Additionally many deterrents have been eliminated

by the ingenuity and resourcefulness of workers in many fields Ample supplies are readily available costs have been reduced crystalline preparations possess great stability oral administration is practicable and several satisfactory repository methods provide prolonged levels from infrequent injections permitting ambulatory treatment

Dynamics of Penicillin Action

During early days of penicillin therapy when supplies were insufficient and unit cost was a distinct factor in estimating dosage schedules it was an understandable and justifiable policy to use minimum effective amounts of antibiotic In order to obtain a measurable yardstick for guidance efforts were made to determine exact penicillin blood levels required for bactericidal activity and then to estimate the amount of penicillin needed to achieve these levels In this way maximum use was made of invaluable material and the greatest numbers of individuals were treated with as little wastage as possible

After penicillin supplies increased the majority of clinicians found themselves in agreement with opinions stated in the first edition of The Integrated Practice of Medicine These held that dosage tables for penicillin called for quantities that are altogether too small and Some of the early disappointments of penicillin therapy can be attributed to small dosage rather than to insensitivity to the therapeutic agency Thus the original dosages used for gonorrhea and syphilis respectively were 60 000 and 1 200 000 units Our practice is to use in gonorrhea 500 000 to 1 000 000 units and in syphilis no less than 10 000 000 units (p 107) Increasing clinical experience and additional laboratory information have served to favor the principle of penicillin overdosage now made possible by *availability* of vast supplies sold at incredibly low costs considering the therapeutic potential of the antibiotic At the same time it has become apparent that determinations of penicillin blood levels (never practicable for the private practitioner) may be quite misleading as guides to therapy

Many clinical impressions based merely on pragmatic experience found laboratory corroboration in Jawetz s study of the dynamics of the action of penicillin (Arch Int Med 81 203 1948) This important work may be summarized in the following general statements

1 Single large injections suffice to cure many experimental infections
2 Smaller doses to be equally effective must be repeated at frequent intervals over a longer period of time
3 The effects of penicillin persist beyond the duration of measurable blood levels For example penicillin may be detected in the blood for only an hour but its effects may be measured bacteriologically for six to eight hours
4 Prolonged effect of penicillin after absence of detectable amounts in blood is due to persistence of antibiotic in tissues Here invading bacteria may be (a) unable to reproduce due to damage to enzyme systems or (b) they may be rendered more susceptible to bodily defenses such as phagocytosis
5 Reliance on penicillin blood levels may be misleading in two

ways (a) bactericidal activity may persist in tissues despite absence of detectable levels of antibiotic in circulating fluid (b) there may be detectable levels of antibiotic in blood and even sterilization as attested by negative blood cultures yet bacteria may continue to grow in tissues

These views are offered in confirmation of the policies that penicillin must be administered in a priming dose vastly in excess of the indicated need and that antibiotic must be continued beyond the seemingly indicated required span of time

Varieties

Recognition identification and analyses of at least four sub-groups of penicillin have resulted in (1) elimination of less effective varieties especially penicillin F and (2) establishment of crystalline penicillin G as the standard for therapeutic efficacy

Master Standard

The penicillin master standard adopted by the Federal Food and Drug Administration is the crystalline sodium salt of penicillin G of a potency of 1 650 units per milligram as determined on the basis of many assays made by leading manufacturers of penicillin and by the Northern Regional Research Laboratory

VARIETIES OF PENICILLIN

Penicillin F (2 pentenyl penicillin)

Only 1/6th as effective as crystalline penicillin G in treatment of syphilis.

Penicillin K (heptyl penicillin)

Less effective than penicillin G in syphilis Mixtures limited to 30% content by Food and Drug Administration

Penicillin X (p-hydroxybenzyl penicillin)

Less dependable than crystalline penicillin G except in gonorrhea

Penicillin G (benzyl penicillin)

Most effective in syphilis Prefer to penicillin F K or X Available in crystalline form as salts of sodium potassium or procaine May be injected in aqueous solution aqueous suspension, suspension in oil suspension in oil and white wax or beeswax, or suspension with 2% aluminum monostearate Eliminates reactions due to impurities Lessens antigenic threat in hypersensitivity reactions Eliminates variations in treatment results due to admixture with varieties of lesser potential such as penicillin F in syphilis

Salts

Salts of aluminum calcium potassium sodium and procaine penicillin have been prepared For parenteral introduction crystalline sodium potassium or procaine salts of penicillin G are distinctly favored over amorphous calcium and sodium derivatives The aluminum salt may be preferred for oral use

SALTS OF PENICILLIN

Calcium Penicillin (Amorphous) Sodium Penicillin (Amorphous)

Require refrigeration even in dry state solution stable only three to s ven hours somewhat le s expensive than crystalline salts of sodium and potassium penicillin G but not sufficient to compensate for other shortcomings

Aluminum penicillin

Advocated only for oral use not inactivated in stomach acid insoluble gradu ally dissolves in alkaline medium Absorbed with maximum utilization of dose Results comparable to similar amounts injected parenterally May prove oral product of choice

Sodium Penicillin (Crystalline) Potassium Penicillin (Crystalline)

Stable in dry state at room temperatures Water soluble Prefer to unstable amorphou mixtures Use as cry talline sodium or pota sium penicillin G for ointments troches aerosols suppo itories tablets aqueous solutions and oil suspensions with or without white wax or beeswax and with or without 2% aluminum monostearate Prefer to procaine penicillin G for immediate effect after parenteral introduction U e exclu ively for intravenous intrathecal or intraventricular introduction Prefer procaine penicillin G for prolonged levels

Procaine Penicillin G (Crystalline)

Stable at room temperature Relatively insoluble in water Prefer to amorphous preparations Yield to crystalline sodium or potassium alts for local topical and oral administration for immediate levels after parenteral injection and for intravenous intrathecal and intraventricular introduction Otherwise paren teral preparation of choice for prolonged levels economy and efficiency Use aqueous suspension for 24 hour level oil suspensions for 48 hour levels and oil suspensions with 2% aluminum monostearate for 96 hour levels. Compensate for early lag by combining 100 000 units crystalline sodium or potassium with first 300 000 units procaine G

Vehicles and Accessories Used in Parenteral Penicillin Therapy

For the most part newer vehicles and accessories for parenteral penicillin therapy have been introduced for the purpose of maintain ing prolonged blood and tissue levels when using rapidly excreted sodium and potas ium salts of penicillin These latter were first sus pended in oil with white wax or beeswax for slow release from tissue deposits then aluminum monostearate was added further to delay absorption and finally an effort to accomplish the same end by a different mechanism was responsible for development of carinamide staticin which through production of a renal blockade prevented overly rapid penicillin excretion by the kidneys

The popularity of these early and ingenious efforts to prolong anti biotic activity diminished with introduction of slowly soluble procaine penicillin G whose aqueous su pensions are capable of sustaining therapeutic levels for a period of at least twenty four hours and whose oily suspensions with 2% aluminum monostearate provide effective bactericidal efficacy for the majority of pathogens for as long as ninety six hours

VEHICLES AND ACCESSORIES FOR PARENTERAL PENICILLIN THERAPY

Aqueous Solutions

Isotonic saline dextrose molar lactate or distilled water Solutions of crystal line sodium or potassium penicillin G stable at room temperature at least eight hours and twenty four hours in the refrigerator Use ordinary 2 cc hypodermic syringes and needles Injections painless Drying of syringe unnecessary Cleansing with chemicals not required Prompt but transitory levels require repetition after 3 or 4 hour intervals night and day

Aqueous Suspensions (Shake well before use)

For relatively water insoluble procaine penicillin G Use ordinary 2 cc syringe with 20 gauge needle Drying of syringe unnecessary Cleansing with chemi cals not required Levels sustained beyond twenty four hours Mixtures of 300 000 units of crystalline procaine penicillin G and 100 000 units of crystal line sodium or potassium penicillin G provide prompt and sustained blood and tissue levels

Oil Suspensions (Shake well and warm before use)

In peanut or sesame oil Require dry syringe and needles of 18 gauge Injec tions may be painful Hazard of oil embolization remote but possible Re idual infiltrations not uncommon Oil suspensions of crystalline sodium or potassium penicillin G give no more sustained levels than aqueous suspensions of crystal line procaine penicillin G

Oil Suspensions with White Wax or Beeswax (Shake well and warm before use)

Combine peanut or sesame oils with 4 8% (w/v) white wax U S P or beeswax (Romanowsky formula) Suspend amorphous or crystalline sodium or potassium penicillin G for 24 to 72 hour levels Not advised because of difficulties of administration, dangers of injection frequency of local infiltrations require ment of dry needle and syringe and necessity to cleanse with alcohol and acetone mixtures For 24 hour levels prefer aqueous suspensions of crystalline procaine penicillin G For 24 to 96 hour levels prefer crystalline procaine penicillin G in oil with 2% aluminum monostearate (see below)

Oil Suspensions with 2% Aluminum Monostearate (Shake well and warm before use)

Peanut or sesame oil suspensions As above Same technical difficulties and hazards Use for cry talline procaine penicillin G when 96 hour level is required

Pendil

Sterile preparation of cholesterol derivatives in peanut oil to prolong peni cillin action Obsolete since introduction of procaine penicillin G

Carinamide Staticin

For production of renal blockade Give 4 to 8 half gram tablets every four hours (p 4275) Obsolete since introduction of crystalline procaine penicillin G

Romanowsky Formula

Oil suspension with wax.

Vehicles of Choice for Parenteral Penicillin Therapy

Immediate Level Intramuscular or intravenous aqueous crystalline sodium or potassium penicillin G

Intravenous Injection Aqueous crystalline sodium or potassium penicillin G

Intrathecal or Intracisternal Introduction Instill 10 000 to 20 000 units of crystalline sodium or potassium penicillin G in 10 to 20 cc of physiologic saline after withdrawal of slightly greater amount of cerebrospinal fluid May cause *aseptic meningitis (p 4409)*

24 Hour Level Intramuscular aqueous suspension of crystalline procaine penicillin G

Immediate and Sustained 24 Hour Level Intramuscular aqueous suspension of crystalline sodium or potassium penicillin G (100 000 units) with crystalline procaine penicillin G (300 000 units)

48 Hour Level Intramuscular oil suspension of crystalline procaine penicillin G

72 to 96 Hour Level Intramuscular oil suspension of crystalline procaine penicillin G with 2% aluminum monostearate

Available Products

Pharmaceutical manufacturers may point with pride to their achievements in penicillin therapy Since lifting governmental restrictions supplies of antibiotic exceed even the stupendous demands present costs are a small fraction of introductory prices crystallization of penicillin G guarantees stability and uniformity of product and oil suspensions additions of 2% aluminum monostearate and preparations of procaine penicillin G have eliminated the necessity for frequent injections

Penicillin currently can be given by inunction aerosolization instillation sublingually orally rectally intravaginally subcutaneously intramuscularly intravenously into cavities intrathecally intraventricularly and presumably intraurethrally if necessary The grateful therapist who once pleaded and cajoled for each 1000 units now finds himself bewildered by the variety of available preparations These include Council accepted products as well as so called specialties with registered trade names and ingenious packaging devices

APPROVED PENICILLIN PRODUCTS

Purpose	Preferred Product	Comment
TOPICAL APPLICATION		
Skin Ointment	Crystalline potassium penicillin G N N R (Lilly) 1 gm = 1000 units	Because of high incidence of hypersensitivity reactions prefer bacitracin or tyrothricin
Ophthalmic Ointment	Crystalline potassium penicillin G N N R (Squibb) 1 gm = 100 000 units	Prefer aureomycin ointment which has broader bacterial spectrum and less risk of sensitization
Troches	Calcium penicillin N N R (Squibb)	Prefer tyrozets (tyrothricin) to avoid penicillin sensitization
	Crystalline sodium or potassium penicillin G N N R (Premo C S C) 50 000 unit tablet	Prefer bacitracin or tyrothricin to forestall sensitization to penicillin which may preclude parenteral administration at later date when need is greater

biotic activity ...
penicillin G whose
therapeutic levels for
oily suspensions wit
bactericidal efficacy

APPROVED PENICILLIN PRODUCTS (*Continued*)

Purpose	Preferred Product	Comment
Inhalators	Crystalline sodium penicillin G in cartridges (Abbott) or dispolator (Squibb)	Especially useful for self treatment, if risk of sensitization appears warranted
Suppositories (Vaginal)	Calcium penicillin N N R. 100 000 and 250 000 units (Bristol Schenley)	Large unitage suggests postabsorptive effects Prefer parenteral injection
ORAL		
Tablets	Aluminum penicillin 50 000 units (Hynson)	For self treatment, use quadruple parenteral doses
	Crystalline potassium penicillin G N N R 100 000 250 000 and 500 000 units (C S C Upjohn)	Repeat every three or four hours
Powder	Crystalline procaine penicillin G (Lederle Spersoids) One rounded teaspoonful = 50 000 units	Palatable preparation for infants and children
PARENTERAL		
Aqueous Solutions	Crystalline sodium or potassium penicillin G N N R 100 000 200 000 500 000 1 000 000 unit vials (Abbott, Bio Ramo CSC Dwight, Lilly Premo Pfizer Schenley Squibb)	All purpose preparations for subcutaneous intramuscular intravenous intracavitary intrathecal or intraventricular u e Require repetition every three or four hours
Aqueous Suspensions (intramuscular only)	Crystalline procaine penicillin G N N R 1 cc = 300 000 units (Bristol CSC Lederle Parke Davis Squibb Upjohn)	Effective levels up to twenty four hours after one hour lag
	Crystalline procaine penicillin G with crystalline potassium penicillin G 300 000 units of former to 100 000 units of latter (Bristol C S C Lederle Parke Davis Squibb Upjohn)	Ideal for immediate and sustained levels up to twenty four hours
Oil Suspensions (intramuscular only)	Crystalline procaine penicillin G N N P 1 cc = 300 000 units (Merrell Premo Pfizer Squibb)	After lag effective levels for forty-eight to seventy two hours Oil deposits may cause sterile abscesses and prolonged hypersensitivity reactions
	Crystalline procaine penicillin G in oil with 2% aluminum monostearate N N P (Abbott C S C Premo Squibb)	As above but levels for seventy two to ninety six hours
	Crystalline procaine penicillin G and crystalline potassium penicillin G 1 cc = 300 000 units of former and 100 000 of latter with 1 5% aluminum monostearate (Bristol)	Immediate and sustained levels to seventy two to ninety six hours

Summary

The undernoted practical points merit consideration in the practical therapeutics of penicillin

1 Of the varieties of penicillin choose penicillin G (benzyl peni

cillin) Reject products derived from penicillin F penicillin K or penicillin X

2 Of the salts of penicillin choose crystalline sodium potassium aluminum or procaine penicillin G Avoid amorphous calcium or sodium penicillin except for reasons of economy

3 Avoid carinamide staticin Prefer to sustain levels with crystalline procaine penicillin G in aqueous or oily suspension the latter with or without 2% aluminum monostearate

4 Avoid topical applications if possible They give a higher percentage of sensitivity reactions (p 4136) and may preclude later use of penicillin when need is more urgent Prefer local use of bacitracin (p 4247) or tyrothricin (p 4622) for which there are no present parenteral indications

5 Avoid troches local sensitization is quite frequent and resulting glossitis may prove embarrassing to respiration

6 If ointments suppositories or troches must be used prefer crystalline sodium or potassium penicillin G

7 For oral use investigate claim that aluminum penicillin is as effectual orally as crystalline salts of sodium and potassium parenterally Until proven however give oral doses in four times the unitage indicated parenterally Oral doses of 100 000 units every three hours maintain blood levels approximating 0 03 to 0 5 units per cc of serum These are sufficient to sterilize cultures of gonococci hemolytic streptococci and pneumococci they are insufficient for many meningococci staphylococci and most anhemolytic streptococci

8 Even if claims for aluminum penicillin are confirmed use oral products sparingly The unit cost almost equals parenteral larger doses offset the economy absorption is irregular sensitization is more frequent

9 For inhalation prefer bacitracin or tyrothricin for reasons indicated above Precede aerosolization by instillation of vasoconstrictor such as 0 05% privine or 0 25% neosynephrine

10 Quite likely the efficacy of vaginal suppositories results from postabsorptive activity since unitage is great Under these circumstances it is better to substitute parenteral injections since absorption is more certain and levels are probably better sustained

11 Try to avoid deposits of penicillin that produce significant levels beyond twenty four hours However if it is necessary to sustain levels use crystalline procaine penicillin G in sesame oil with 2% aluminum monostearate Prefer sesame to peanut oil It is less allergenic

12 Avoid suspensions with white wax or beeswax They are cumbersome to inject they require dry needles and syringes they may produce local induration necrosis and hypersensitivity reactions

13 For rapid levels inject aqueous solutions of crystalline sodium or potassium penicillin G intramuscularly or intravenously

14 For intrathecal or intracisternal administration use aqueous solutions of *crystalline sodium or potassium penicillin G* Remember that intrathecal penicillin may cause aseptic meningitis and that equally effective cerebrospinal fluid levels may be achieved with greater ease and safety by massive parenteral injections

15 For 24 hour levels inject aqueous suspensions of crystalline procaine penicillin G Shake these suspensions well before use

16 To compensate for lag of one hour following injection of each 300 000 units of crystalline procaine penicillin G add 100 000 units of crystalline sodium or potassium penicillin G to the priming dose This combination of crystalline sodium or potassium penicillin G with crystalline procaine penicillin G in aqueous suspension approaches the ideal for the private practitioner It can be given with a freshly boiled hypodermic syringe 1 or 2 cc provides a combined unitage of 400 000 or 800 000 units respectively injections each twenty four hours assure effective maintenance levels hypersensitivity phenomena are not prolonged by long-deferred absorption

Bacterial Spectrum

With increasing experience the broad spectrum of antibiotic activity claimed for penicillin (p 111) has been amply substantiated With the possible exception of meningococcemia it has replaced sulfonamides (Table 14 p 113) in the treatment of coccal infections both gram negative and gram positive As a treponemicide especially in syphilis its preeminence is unchallenged In the management of gram positive bacillary invasions its effects are far from satisfactory and supplementation with antitoxic and antibacterial serums is mandatory Finally in certain diseases such as psittacosis where penicillin was deemed worthy of trial for lack of something more potent to employ it has yielded to the clearly specific results obtained with aureomycin and chloramphenicol

Staphylococci With few exceptions staphylococci are penicillin sensitive resistant strains may develop they are best treated by initial massive dosage and by continued and sustained high therapeutic levels supplemented with aureomycin chloramphenicol sulfonamides or one of the streptomycins

Streptococci With few exceptions notably anaerobic strains streptococci are penicillin sensitive resistant strains may develop they are best treated by initial massive dosage and by sustained high blood and tissue levels together with supplementation using aureomycin chloramphenicol or one of the streptomycins combinations with sulfonamide are best avoided since the latter may produce tuberculin type hypersensitivities (p 4169) including the syndromes of rheumatic fever and periarteritis nodosa

Pneumococci Almost all strains of pneumococci are remarkably penicillin sensitive supplementation is rarely required unless there is a superimposed or accompanying virus pneumonitis (p 4636) under such circumstance add aureomycin or chloramphenicol

Meningococci Although most meningococci are penicillin sensitive many clinicians prefer sulfonamide to penicillin as the antibiotic of choice because of the gravity of the infection it is recommended that both antibiotics be used with supplementary aureomycin or chloramphenicol if necessary

Gonococci Gonococci are remarkably penicillin sensitive rarely is supplementation required when needed aureomycin chloramphenicol streptomycin or sulfonamide can be added or substituted

B anthracis Anthrax is a grave disease that does not respond wholly satisfactorily to penicillin large initial doses are required high levels must be maintained and sustained for a considerable period of time Additional injections of antibacterial serum are required and supplementation with aureomycin or chloramphenicol if necessary

Cl tetanus Tetanus is a grave disease which does not respond satisfactorily to penicillin alone large initial doses are required high levels must be maintained and sustained during injection of large unitages of antitoxin

Cl perfringens Gas gangrene is a grave infection in which the results of penicillin therapy are far from satisfactory large doses must be deposited initially high concentrations must be maintained and sustained while massive unitage of antitoxin is injected simultaneously

Co diphtheriae Diphtheria is a grave infection which responds less than satisfactorily to penicillin large initial doses are required high levels must be maintained and sustained while massive unitage of antitoxin is injected simultaneously

Cl botulinum Botulism is a grave infection which responds less than satisfactorily to penicillin large initial doses are required high levels must be maintained and sustained while massive unitage of antitoxin is injected simultaneously

Erysipelothrix rhusiopathiae Erysipeloid responds specifically to penicillin supplementation is not required

Treponemes Most spirochetes are penicillin sensitive though resistant strains are encountered large initial doses are required with maintenance of high tissue levels for at least two or three weeks because of tendency of spirochetal diseases to relapse consider re treatment after a few weeks or months to obtain best results in syphilis frambesia pinta fusospirochetosis relapsing fevers and certain rat bite fevers

Psittacosis Penicillin results are less than satisfactory by contrast aureomycin and chloramphenicol appear definitively specific

Actinomycosis In this and other systemic fungus invasions massive and sustained doses of penicillin are given as a desperation remedy in concert with vaccine sulfonamide and other antibiotics as indicated

E histolytica Combination of penicillin and amebacides is followed by fewer relapses than when specific is given alone since penicillin is not amebacidal better results are attributed to elimination of penicillin sensitive secondary invaders permitting amebacide to function with greater efficiency superior results noted with aureomycin alone and in combination with amebacides

Penicillin and Other Antibiotics

The status of penicillin relative to other antibiotics may be summarized in the following statements

1 For local use prefer bacitracin or tyrothricin
2 As against sulfonamide prefer penicillin Its lesser hazard counts

heavily in its favor against the toxicity and hyperallergenicity of sul fonamide (p 4179)

3 In the treatment of infections due to organisms sensitive alike to penicillin and to aureomycin-chloramphenicol choose penicillin Cur rently costs are lower ease of parenteral introduction assures greater uniformity of action and self treatment is discouraged

4 In the treatment of infections sensitive alike to streptomycin and penicillin choose penicillin for its lesser toxicity

5 For combined antibiotic effects prefer penicillin and aureomycin chloramphenicol The combination covers the bacterial spectrum easily and effectively No known antibiotic sensitive microbic invaders are omitted other than malarial parasites and trypanosomes

Toxicity and Anti Therapeutic Devices

Against the monumental therapeutic achievements of penicillin the threat of untoward responses is inconsequential In point of fact much earlier reported toxicity was the result of impurities eliminated since introduction of crystalline penicillin and others were due to the use of vehicles such as waxes now virtually obsole cent.

Pharmacologic Toxicity

Penicillin has apparently no consistent pharmacologic toxicity Amounts as great as 30 000 000 units a day have been given repeatedly without untoward re ponses

Hypersensitivity Manifestations

Penicillin like every other protein molecule is capable of inducing allergic hypersensitivity reactions Estimates of their frequency vary from a low of 2 per cent to a high of 15 per cent The discrepancy between reports undoubtedly is due to the presence of many variables which include (a) impure earlier mixtures of amorphous penicillin before crystallization was accomplished (b) antigenic responses to vehicles such as beeswax white wax peanut and sesame oil (c) sensi tivity to procaine in the currently popular crystalline salt of procaine penicillin G (d) toxic manifestations due to other drugs given during the course of a serious illne s

Studying parenteral administration exclusively Lepper and his col leagues (J Clin Invest 28 826 1949) noted slightly over 1 per cent reactions using low or moderate doses of aqueous crystalline solutions but almost 3 per cent with an oil and beeswax menstrum With high doses given for long periods the reactive rate rose to 7 8 per cent with aqueous crystalline solutions Reactions were particularly frequent in patients with histories of previous allergy or prior exposure to penicillin

Chronic Tuberculin type Hypersensitivity No instance of tuberculin type hypersensitivity has thus far been reported as the result of peni cillin therapy This clear record is in sharp contrast to that of sulfonamide

Gonococci Gonococci are remarkably penicillin sensitive rarely is supplementation required when needed aureomycin chloramphenicol streptomycin or sulfonamide can be added or substituted

B anthracis Anthrax is a grave disease that does not respond wholly satisfactorily to penicillin large initial doses are required high levels must be maintained and sustained for a considerable period of time Additional injections of antibacterial serum are required and supplementation with aureomycin or chloramphenicol if necessary

Cl tetanus Tetanus is a grave disease which does not respond satisfactorily to penicillin alone large initial doses are required high levels must be maintained and sustained during injection of large unitages of antitoxin

Cl perfringens Gas gangrene is a grave infection in which the results of penicillin therapy are far from satisfactory large doses must be deposited initially high concentrations must be maintained and sustained while massive unitage of antitoxin is injected simultaneously

Co diphtheriae Diphtheria is a grave infection which responds less than satisfactorily to penicillin large initial doses are required high levels must be maintained and sustained while massive unitage of antitoxin is injected simultaneously

Cl botulinum Botulism is a grave infection which responds less than satisfactorily to penicillin large initial doses are required high levels must be maintained and sustained while massive unitage of antitoxin is injected simultaneously

Erysipelothrix rhusiopathiae Erysipeloid responds specifically to penicillin supplementation is not required

Treponemes Most spirochetes are penicillin sensitive though resistant strains are encountered large initial doses are required with maintenance of high tissue levels for at least two or three weeks because of tendency of spirochetal diseases to relapse consider re treatment after a few weeks or months to obtain best results in syphilis frambesia pinta fusospirochetosis relapsing fevers and certain rat bite fevers

Psittacosis Penicillin results are less than satisfactory by contrast aureomycin and chloramphenicol appear definitively specific

Actinomycosis In this and other systemic fungus invasions massive and sustained doses of penicillin are given as a desperation remedy in concert with vaccine sulfonamide and other antibiotics as indicated

E histolytica Combination of penicillin and amebacides is followed by fewer relapses than when specific is given alone since penicillin is not amebacidal better results are attributed to elimination of penicillin sensitive secondary invaders permitting amebacide to function with greater efficiency superior results noted with aureomycin alone and in combination with amebacides

Penicillin and Other Antibiotics

The status of penicillin relative to other antibiotics may be summarized in the following statements

1 For local use prefer bacitracin or tyrothricin
2 As against sulfonamide prefer penicillin Its lesser hazard counts

comparable bac'eric dal activity but do not u_e sulfonamide Prefer aureomycin or chloramphenicol if possible

5 If the history of sensitivity is positive but skin test is negative proceed with penicillin therapy but give a prophylactic injection of 5 cc of 1% benadryl (50 mg) at least fifteen to twenty minutes before depositing antib otic

6 If patient gives a definite hi_tory of hypersen_itivity to prior u_e of penicillin try to avoid admini_tration of offending allergen Preferably substitute aureomycin or chloramphenicol

7 If penicillin must be used de ensitize as with other allergens Inject a 1/1000 _olution intracutaneously and increa_e the dose from 0 1 to 1 cc if possible using increments of 0 1 cc every ten to fifteen minutes Pepeat with 0 1 cc of 1 100 _olution and try to work up to appreciable unitage by slow degrees meantime forcing antihistamines

Bacterial Re_istance

The development of active immunity by micro-organi_ms as the result of antibiotic therapy attests again to the ingenuity of the foes of man Bacterial resistance or fastne s is commonly exhibited to sulfonamides (as for example by gonococci) and to streptomycin (by tubercle bacilli) Bacterial resistance to penicillin most often has been encountered in streptococcal and staphylococcal invasions For this reason it is wise to give ma_sive priming doses o that both highly sensitive and more resistant strains of invading micro-organism are immobilized and to continue treatment for a prolonged period of time o that isolated nests of lurking in_ensitive bacteria in relatively remote tissue areas are finally overcome

Herxheimer Reactions

The Jari_ch Herxheimer reaction occurs in the treatment of many di ea_es but most particularly in syphilis Following first injection of therapeutic agent whether arsenical or penicillin there is noted a febrile reaction often with inten_ification of pre-existent symptomatology

Herxheimer reactions have been reported as the result of penicillin therapy particularly in chronic brucellosis and in late syphilis both cardiova_cular and neurologic A febrile Herxheimer reaction was observed in 34 per cent of 349 patients with various types of neurosyphilis Simultaneously there was increase in the numbers of cells of the spinal fluid and in its protein content

For prevention of Herxheimer reactions the following precautions are sugge ted

1 precede penicillin therapy of cardiovascular or neurologic syphilis by 6 to 10 injections of bismuth subsalicylate (p 4255)

2 start with initial injections of penicillin not to exceed 10 mg per kilo (700 units for the average adult weighing 150 lbs) Increase dose to 1 000 2 000 5 000 10 000 50 000 and 100 000 units

3 preceding and concurrently with penicillin therapy use antihistamine at first parenterally and later orally

which has demonstrably produced lesions of rheumatic fever and peri arteritis nodosa in experimental animals and presumably in the human (p 4169)

Acute Histamine type Hypersensitivities Penicillin may cause any of the long list of acute histamine type hypersensitivity manifestations (p 4167) Most often these occur locally at the site of a topical application less frequently the allergic reaction is a post absorptive response

In approximately 5 to 15 per cent of patients local application of a penicillin product is followed sooner or later by some variety of contact dermatitis (p 4297) This may take the form of erythema localized pruritus vesicular pustular or exfoliative reaction urticaria or angioneurotic edema Similar reactions may occur in the conjunctiva following use of ophthalmic ointment or of drops containing antibiotic Oral products particularly troches and tablets may result in serious topical manifestations since the resulting glossitis angioneurotic edema of the tongue uvula pharynx or larynx may cause obstruction to respiration Intrathecal instillations may produce aseptic meningitis with pleocytosis and accompanying malaise headache dizziness vertigo nausea vomiting muscle spasms and in extreme instances convulsions or coma

The frequency of histamine type manifestations following local or topical application of penicillin products is the basis for recommendation that administration of penicillin be limited to parenteral introduction Bacitracin or tyrothricin which have somewhat similar antibacterial properties may be substituted locally since neither of these products is seemingly as allergenic as penicillin and neither can be given parenterally because of inherent toxicity

Postabsorptive histamine type hypersensitivity manifestations of penicillin resemble those produced by other allergens They include diffuse morbilliform scarlatiniform erythematous vesicular bullous and exfoliative eruption urticarias angioneurotic edema eosinophilia arthropathy nausea and vomiting abdominal cramps malaise headache drug fever dizziness vertigo muscle twitching convulsions and loss of consciousness etc

Prevention and Treatment of Hypersensitivity Reactions Prevention and treatment of hypersensitivity due to penicillin may be accomplished by obedience to the following tenets

1 Avoid local and topical uses of penicillin Substitute bacitracin or tyrothricin if possible

2 Do not prescribe or administer penicillin until a history of hypersensitivity has been taken (p 4187)

3 Even if there is no history of hypersensitivity give prophylactic doses of antihistamine concurrently with penicillin and for two weeks after cessation of antibiotic Prescribe 200 mg daily of pyribenzamine or benadryl (p 4216)

4 If patient gives history of hypersensitivity to antigens other than penicillin perform a penicillin skin test before making therapeutic injection If the skin test is positive substitute products of other manufacturers If these are allergenic consider use of another antibiotic of

respiratory tract kidneys nervous system and eyes (p 1028) particularly if associated with generalized dermatoses and an eosinophilic leukocytosis

5 Get history of previous hypersensitivity (p 4187) Note exposure to infection or drug allergens particularly sulfonamide dilantin aspirin and other analgesic antipyretics hypnotics etc

6 To establish diagnosis do not hesitate to biopsy nodule infiltrated vessel or indurated muscle

7 Institute therapy with antihistamines using daily doses approximating 800 mg of pyribenzamine or benadryl

8 Until preparations are commercially available make application for cortisone to Merck and Co Rahway N J or to Dr Chester S Keefer Chairman National Academy Allocation Committee 2101 Constitution Ave Washington D C for ACTH to Dr John R Mote Armour and Co Chicago Illinois Meantime make clinical trials of artisone (Wyeth) and percorten (Ciba) purchaseable in the open market. In the use of the latter inject 1 cc intramuscularly (equivalent to 5 mg desoxycorticosterone) followed within five minutes by intravenous introduction of 10 cc of 10% ascorbic acid (1 gm) Unless prompt and dramatic improvement is noted with artisone and percorten—ascorbic acid abandon therapy after three or four consecutive daily injections

9 Avoid administration of any potential allergen and particularly of sulfonamide

PERIODIC DISEASE

Principles of Diagnosis and Therapy

1 Hobart Reiman (J A M A 141 175 1949) has collected a remarkable group of patients who suffered periodic but benign febrile disorders over the course of many years

2 In general the syndromes arranged themselves in four groups including periodic fever periodic abdominalgia (benign paroxysmal peritonitis) periodic or psychic neutropenia and periodic or intermittent arthralgia

3 In addition to the main groups there were also certain forms of anaphylactoid purpura angioneurotic edema and periodic paralysis

4 Despite the numbers of attacks none of these patients suffered inroads on their general health All were otherwise in excellent physical condition

5 The cause for periodic disease is presently unknown The several theories that have been advanced include unknown infection allergic hypersensitivity endocrinologic imbalance migraine and epilepsy Reimann regards these theories as inadequate and suggests that until further knowledge is attained it is simplest to regard periodic disease as a manifestation of the rhythm of life

6 Periodic disease is never recognized in an initial episode Later

PENICILLIOSIS

The penicilliosis mold is capable of producing otomyco i (p 3305) and pulmonary absce.ses (Fig 506 p 2213) resembling those result ing from aspergillosis infections

Treatment is conducted in the manner outlined for the latter (p 4241)

PENTAQUINE (SN 13276)

Pentaquine 6 methoxy 8 (5 isopropyl amino amylamino) quinoline monophosphate has earned a present niche in the treatment of malaria through its efficacy in synergistic combination with quinine in the treatment of relapsing vivax infections refractory to chloroquine and chlorguanide (p 4398)

Available Products

Pentaquine Phosphate (Abbott) Tablets 10 mg of pentaquine ba e containing 13 3 mg of *pentaqu ne phosphate*

Pentaquinine and Quinine (Abbott) Tablets of 18 mg of former and 0 3 gm quinine sulfate

Therapeutics

In the treatment of relapsing vivax infections the undernoted routine approximates 100 per cent cure

Pentaquine 10 mg and quinine sulfate 0 5 gm three times daily for fourteen days Pentaquine should not be given to children and must be u ed cautiously in adults that are not light skinned

Toxicity

See Quinine (p 4486)

PERI ARTERITIS NODOSA

Principles of Diagnosis and Therapy

1 Regard peri arteritis nodosa as a chronic tuberculin type allergic hyper.ensitivity with e.sential changes in peripheral va.cular system (Fig 225 p 1028)

2 Note accompanying change. throughout mesenchymal collagen tissues

3 Observe increase in incidence of periarteritis nodo a at autopsy since introduction of sulfonamide therapy Nevertheles nonfatal exam ples have been observed

4 Suspect peri arteritis nodosa in all instances of abacterial pro tracted pyrexia with diffuse manifestations involving peripheral ve.sels

AVAILABLE PERTUSSIS VACCINES

Product	Billions H. pertussis per cc	Remarks
Pertussis Vaccine (Squibb Upjohn)	10	6 cc for full immunization
Pertussis Vaccine (Parke Davis Wyeth)	15	4 cc for full immunizing dose
Pertussis Vaccine (Cutter National Drug Squibb Sharp & Dohme)	20	3 cc for full immunizing dose
Pertussis Vaccine Alum Precipitated (Sauer Parke Davis)	30	2 cc for immunizing dose Preparation of choice for single immunization.
Pertussis Vaccine Alum Precipitated, Diphtheria Toxoid Alum Precipitated Combined (Upjohn Sharp & Dohme)	10	6 cc for full immunizing dose
Pertussis Vaccine Diphtheria Toxoid Combined (Parke Davis)	15	4 cc for full immunizing dose
Pertussis Vaccine Diphtheria Toxoid Alum Precipitated Combined (National Drug)	30	2 cc for full immunizing dose Preparation of choice for double immunization.
Pertussis Vaccine Alum Precipitated, Diphtheria Toxoid, Alum Precipitated Tetanus Toxoid Alum Precipitated Combined (National Drug Squibb)	30	Preparation of choice for triple immunization

Practical Management

Prophylaxis

1 Favor active immunization preferably before the age of six months Introduce at least 45 million organisms in three injections at intervals of four to six weeks For routine use advocate triple immunization with diphtheria toxoid (alum precipitated) tetanus toxoid (alum precipitated) pertussis vaccine Note variation in bacterial count of available pertussis vaccines (p 4463) Supplement triple vaccine if necessary with plain pertussis vaccine to bring total pertussis bacterial count to 45 billion organisms

2 For booster doses every two or three years in early life and at five year intervals in later life or upon contact introduce 10 to 15 billion organisms preferably using the Parke Davis preparation of which 1 cc contains 30 billion H pertussis phase I (Sauer strain) alum precipitated

3 For protection of those heavily exposed in the lag period between injection of vaccine and development of a high antibody titer choose between chemoprophylaxis and passive immunization with convalescent human blood or heterologous rabbit serum On all counts prefer chemoprophylaxis with aureomycin or chloramphenicol in amounts approximating 25 mg per kilogram of body weight per day (1 75 gm for average adult weighing 150 pounds)

if all other obvious etiologic factors can be eliminated and repeated episodes are observed with complete recovery the diagnosis may be suspected

7 Without factual experience it is suggested that antihistamine be administered in daily oral doses of at least 200 mg of pyribenzamine or benadryl (p 4216)

PERTUSSIS

[Whooping Cough]

General Principles of Diagnosis and Therapy

1 The importance of whooping cough is vastly underrated in clinical medicine Thus for example the case fatality rate in infants under the age of one year is 25 per cent and 50 per cent of all deaths in the first six months of life occur as the result of whooping cough (p 278)

2 The indifference of the lay public to whooping cough is all the more deplorable since effective agents are available for active and passive immunization and for specific antibiotic therapy of acute phases of the disease

3 It should not be necessary to wait for the characteristic paroxysmal cough The astute parent or physician recognizes pertussis in the catarrhal stage when the patient has merely a persistent irritating non productive cough and a leukocytosis with a predominance of lymphocytes At this time the clinical suspicion may be substantiated by growth of characteristic colonies on cough plates (Fig 40 p 281)

4 For active immunization there are available several pertussis vaccines prepared from phase I organisms These may be plain or alum precipitated they may be combined with diphtheria and/or tetanus toxoid for double or triple immunization (Table p 4362)

5 For passive immunization the Council on Pharmacy has approved a pertussis hyperimmune homologous serum N N R commercially available as Hypertussis (Cutter) in vials containing 2 5 cc In addition the Philadelphia Serum Exchange of 1740 Bainbridge Street Philadelphia 46 Pennsylvania supplies vials containing 20 cc of human lyophilized pertussis immune serum prepared from healthy adults recently recovered from pertussis or recently immunized with phase I vaccine Finally there is a commercially available heterologous (rabbit) hyperimmune antipertussis serum (Squibb Wyeth) This is marketed in vials containing 4 cc with diluted normal rabbit serum for performance of sensitivity tests (p 555) The dose of anti pertussis serum is 4 cc intramuscularly repeated after twenty four hours if necessary

6 Besides products for active and passive artificial immunization H pertussis is sensitive to streptomycin aureomycin chloramphenicol aerosporin and polymyxin With this formidable array of anti infective agents there seems no valid excuse for pertussis to threaten the children of any civilized community

For passive immunization of non sensitive or desensitized allergenic patients deposit 4 cc intramuscularly Repeat after twenty four hours if necessary

14 If paroxysms continue for more than a few days and general nutrition suffers consider setting up an intravenous drip for delivery of protein hydrolysate plasma whole blood and antibiotic

PHYSICAL ALLERGY

Physical allergies due to heat cold and solar energy are being recognized with increasing frequency (p 552) Therapeutic objectives in the management of these allergic hypersensitivities include elimina tion of the ensitizing modality (p 4176) use of sunburn protections (p 3140) in the photosensitive desensitization (p 4191) psychotherapy (p 1316) and palliation or prophylaxis with antihistamines and adren ergens (p 4212)

PINTA

Principles of Diagnosis and Therapy

1 Pinta as other treponematoses yields to arsenicals and penicillin The latter is much preferred because of its lesser toxicity

2 As in the case of frambesia (yaws) principal clinical manifestations of pinta are tegumentary (Figs 51 and 52 p 354)

3 Because of its relatively benign clinical course pinta is treated more in the manner of frambesia than of syphilis A similar penicillin dosage schedule is suggested (p 4558) reserving mapharsen for the penicillin resistant

4 Since serologic reversal may be considerably delayed the efficacy of treatment should not be evaluated until a lap e of at least three months

PITYRIASIS ROSEA

Principles of Diagnosis and Therapy

1 Pityriasis rosea is a generalized dermatosis (Fig 1000 p 3411) that is benign and self limited

2 Local therapy is ineffectual As a matter of fact overenthusiastic management may lead to treatment dermatitis more discomforting than the original dermatosis

3 On the hypothesis that pityriasis rosea is a hypersensitivity mani festation prescribe antihistamines Suggest oral doses of 200 mg daily of pyribenzamine or benadryl If these preparations do nothing else they allay pruritus

Immediate Care

1 For communal prophylaxis isolate the patient with pertussis particularly in the pre paroxysmal stage

2 Give a priming dose of 50 to 100 mg per kilogram of body weight of aureomycin or chloramphenicol (3 5 to 7 gm for average adult weighing 150 pounds) Approximate the lower dosage with aureomycin and the higher with chloramphenicol Suggest that the patient take 2 products every few moments with large amounts of water milk fruit juice tea or bouillon to avoid gastric irritation

3 For infants and children unable to swallow antibiotic improvise a solution or suspension in physiological saline Instill rectally with a catheter and funnel meanwhile pressing the buttocks to prevent expulsion

4 Should it be impossible to introduce antibiotic orally or rectally inject 100 mg aureomycin hydrochloride intravenously in the diluent supplied by the manufacturer Alternatively deposit intramuscularly 1 gm streptomycin

5 Whichever antibiotic is used continue daily maintenance doses equal to the priming dose Divide into 4 equal portions and give at 6 hour intervals by whichever route is tolerated

6 Concurrently with antibiotic and for a period of at least two weeks after the final dose prescribe daily prophylactic antihistamine using 200 mg of pyribenzamine or benadryl in 4 divided amounts

7 Place infant or older child who is desperately ill in an oxygen tent until infection is controlled by antibiotics

8 In severe illness with thick tenacious secretion attempt aspiration of pharynx and trachea with a soft rubber catheter preferably connected to an electrically driven suction apparatus

9 Time honored cough mixtures expectorants and particularly the nauseants do harm and no good in the control of paroxysms Anti spasmodics possess no significant value and may add to patient discomfort through drying of the throat

10 For control of cough choose hycodan bitartrate (p 4416) in the adult dose of 5 mg (1/12 grain) Repeat every four to six hours as needed Avoid codeine and morphine because of side effects (p 3860)

11 Aerosporin and polymyxin reported as beneficial in the treatment of pertussis are not commercially available Each of these products is nephrotoxic *In all likelihood neither is any more effectual than* aureomycin or chloramphenicol

12 For supplementation of antibiotic if needed obtain hyperimmune human pertussis serum If Hypertussis (Cutter) is available inject intramuscularly 2 5 cc Repeat at 24 and 48 hour intervals if necessary If human lyophilized serum can be gotten from the Philadelphia Serum Exchange deposit 5 cc intramuscularly every six to twelve hours for three or four doses Since each of these products is prepared from homologous serum hypersensitivity phenomena need not be feared

13 In desperation resort to heterologous pertussis hyperimmune antiserum derived through immunization of rabbits Make ophthalmic and skin tests with diluted normal serum supplied by manufacturer

econd dose of 1 cc seven to ten days later For booster doses repeat 0 5 to 1 cc as needed preferably biannually

Immediate Care

1 Because of the infectivity of the disease transfer the plague infected patient to a hospital particularly equipped for the care of infectious diseases Notify public health authorities

2 Institute general measures for control of the infected patient (p 67)

3 Warn contacts and nursing attendants of the dangers of the di ease Sugge t active immunization for long term immunity and chemo prophylaxis for protection during lag period between inoculation and development of a sufficiently high titer of antibody For latter purpose prescribe 2 gms daily of sulfadiazine or sulfamerazine

4 Regard sulfadiazine as the drug of choice in the treatment of plague (Platzer U S Naval Med Bull 46 1674) Give a large priming dose orally or intravenously By latter route inject 2 5 gm each of sodium sulfadiazine and sodium sulfamerazine in at least 200 cc of diluent preferably molar lactate For oral priming dose give 3 to 4 gm each of sulfadiazine and sulfamerazine with a tea poonful of bicarbonate of oda

5 Four hours after priming do e of sulfonamide has been admin istered start maintenance dose using 0 5 to 1 gm each of sulfadiazine and sulfamerazine at 4 hour intervals Try to deliver 12 to 30 gm of soluble sulfonamide on the first day of treatment provided that toxic manifestations are not encountered

7 Because of the gravity of the disease combine soluble sulfona mide with streptomycin Make an initial priming intramu cular deposit of 1 to 2 gm continue with 0 5 to 1 gm at 8 to 12 hour intervals as needed

8 Watch for reports of the efficacy of aureomycin and chloram phenicol in the treatment of plague Prepare to substitute either of these non toxic and potent antibiotics for either or both of the products presently advised Becau e of gravity of plague approximate 100 mg per kilogram (7 gm for average adult weighing 150 pounds) for prim ing and daily maintenance do es

9 Concurrently with sulfonamide, streptomycin give oral antihista mines using 200 mg of pyribenzamine or benadryl daily Continue for at least two weeks after the last do e of antibiotic has been administered

10 Tried and found wanting are a variety of therapeutic agents including mercurochrome mercuric phenylate iodides resorcinol mercuric trypan blue quinine arsenicals methylene blue formalin germinin (suramin) merthiolate bacteriophage and penicillin

11 In countries in which unofficial plague antibacterial serum is available injections may be attempted in the patient who is desperately ill or antibiotic resistant After appropriate determinations of sensitivity and de ensitization if necessary introduce intramuscularly or intra venously twenty to forty cc Pepeat every six eight or twelve hours as necessary

PLACENTAL IMMUNE GLOBULIN

Human immune globulin derived from extract of placentas is used in the prophylaxis of measles when gamma globulin connot be obtained

Available Products

Human Immune Globulin (Placental Extract) U S P (Lederle Sharp & Dohme Wyeth)

Therapeutics

For prevention or modification of measles inject intramuscularly 2 to 10 cc Repeat after twenty four to forty eight hour Since human immune globulin of placental origin is a homologous preparation hypersensitivity tests need not be done

PLAGUE

[Bubonic Plague Black Death]

Principles of Diagnosis and Therapy

1 A reservoir of sylvatic plague still exists in flea wild rodents ground squirrels gerbilles marmots and cavies (guinea pigs) The reservoir of human plague persists in house rats sewer rats and ground squirrels (Fig 46 p 320)

2 Plague is transmitted from rodent to rat flea the insect vector and from either of the e reservoirs to man (p 321) Human plague is still encountered in the United States The majority of infections are seen in California but other persistent nests of plague exist in Louisiana Florida Texas and New Mexico

3 Plague may be successfully prevented by active immunization using heat or phenol killed suspensions of P pestis

4 Clinical plague may be actively treated with antibiotics Thus far there has been greatest experience with sulfadiazine and streptomycin By analogy with other infections produced by Pasteurellae notably tularemia it may be expected that aureomycin and/or chloramphenicol will prove equally valuable and less toxic

Practical Management

Prophylaxis

1 Through use of rodenticides (Antu) and insect repellents (DDT *etc* p 4373) attempt to clear area of vectors

2 For active immunization of contacts and those who plan to visit an area in which plague is endemic induce active immunization with *plague vaccine* (Cutter) U S P a sterile solution of P pestis each cc containing 2 billion organisms Inject subcutaneously 0 5 cc Give a

3 Except for pneumococcal conjunctivitis and upper respiratory infections do not rely solely on local therapy For topical use in conjunctivae prefer bacitracin or tyrothricin solutions or ointments Do not hazard sensitization to sulfonamide or penicillin If infection is persistent substitute aureomycin ophthalmic solution and ointment For upper respiratory infections try aerosolization with bacitracin in chloresium

4 In all other pneumococcal infections resort to parenteral introduction of antibiotic Prefer penicillin Inject a loading dose of 600 000 units of crystalline procaine penicillin G in aqueous or oil suspension Maintain antibiotic levels with a similar daily dose injected intramuscularly

5 Concurrently and for two weeks after last dose of antibiotic give prophylactic antihistamine therapy using 200 mg daily of pyribenzamine or benadryl in 4 divided doses

Continuing Care (Unfavorable Course)

1 In overwhelming or persistent infections in bacteremia and in pneumococcal meningitis suspect presence of an undrained feeding focus of diminished patient resistance and/or of increased organism virulence (type III)

2 Obtain specimen for bacteriologic study Identify organism and its subclassification Look for other invading microbes particularly tubercle bacilli fungi and klebsiellas

3 Summon consultant otolaryngologist Particularly look for evidences of spheno ethmoiditis otitis media mastoiditis or sinus thrombosis (p 1447) Prepare for surgical intervention if indicated

4 With diminished patient resistance introduce protein hydrolysate plasma or whole blood

5 Under any circumstance increase level of antibiotic Set up an intravenous drip Introduce massive doses up to 1 million units of crystalline potassium penicillin G in saline every two hours

6 Supplement penicillin with aureomycin or chloramphenicol If stomach is tolerant give immediate loading and daily maintenance doses approximating 100 mg per kilogram of body weight (7 gm for average adult weighing 150 lbs) If stomach is intolerant introduce aureomycin hydrochloride intravenously using 100 to 500 mg of the preparation particularly devised for intravenous use

7 If patient is sensitive to penicillin and/or intolerant of aureomycin and chloramphenicol substitute soluble sulfonamide For intravenous loading and daily maintenance doses give 2 5 gm each of sodium sulfadiazine and sodium sulfamerazine in 200 cc of diluent preferably molar lactate For oral administration give 2 5 gm each of sulfadiazine and sulfamerazine with one teaspoonful of bicarbonate of soda During sulfonamide therapy carefully observe urine and blood for manifestations of drug toxicity

8 With sulfonamide therapy increase dose of antihistamine to 400 mg daily

12 In the era that preceded antibiotic therapy human serum obtained from recent convalescents was highly regarded by those with experience in the treatment of plague Intramuscular injections of 10 to 20 cc repeated after twenty four or forty eight hours were recommended

PNEUMOCOCCAL INFECTIONS

Principles of Diagnosis and Therapy

1 Pneumococci are normal inhabitants of the upper respiratory passages (p 200)

2 Any of the thirty three or more recognizable subtypes of pneumococcus may cause a wide variety of infections including acute rhinitis nasopharyngitis accessory nasal sinusitis tonsillitis tracheobronchitis pneumonitis lobar pneumonia pleuritis conjunctivitis otitis media mastoiditis otogenic and rhinogenic meningitis pneumococcemia bacterial endocarditis osteomyelitis arthritis and peritonitis

3 Except in lobar pneumonia clinical manifestations of pneumococcal infection are not pathognomic (p 2171) Hence the diagnosis *requires bacteriologic identification of the invading microbe* (Fig 22 p 202)

4 Active immunization against the pneumococcus has never proven practicable despite many praiseworthy efforts using pneumonia vaccines combined (Parke Davis) pneumococcus antigen (Lilly) and pneumococcus polysaccharides type specific (Squibb)

5 Pneumococci are strikingly sensitive to penicillin aureomycin chloramphenicol sulfonamides bacitracin and tyrothricin

6 Passive immunization with type specific antipneumococcal *heterologous* serum (equine rabbit) has been rendered obsolete through the response of the pneumococcus to more effectual and less toxic antibiotics

Practical Management

Prophylaxis

1 For *temporary protection after massive exposure to pneumococci* order chemoprophylaxis with oral penicillin Prescribe 250 000 units of crystalline potassium penicillin G in tablet form every six to eight hours for a period of two days or substitute 2 gm daily of sulfadiazine or sulfamerazine in 4 divided doses each given with one teaspoonful of bicarbonate of soda

Immediate Care

1 Institute general measures required for management of the infected patient (p 67)

2 Attempt to isolate bacterium from sputum blood or cerebrospinal fluid Remove just enough of the latter to obtain a specimen

8 The first or prodromal period of systemic invasion is non specific Usually it is not recognized except in immediate contacts Presenting symptoms include ore throat nausea vomiting fever and malaise Physical examination is not revealing Demonstrations of virus or of increase in antibody titer of serum are impractical since even under optimum circumstances laboratory reports cannot be made available until the patient has recovered or succumbed to the disease

9 In all likelihood few of those infected by the poliomyelitis virus progress beyond the systemic phase Quite likely prodromal abortive or inapparent infections confer a naturally acquired active immunity that is as effective as a paralytic attack

10 If this huge reservoir of benign infections is included in statistical studies poliomyelitis may be regarded as an invasion with a high morbidity an extremely low mortality and relatively infrequent sig nificant sequels If on the other hand this huge reservoir of infection is ignored then the disease has a relatively low morbidity a con siderably higher mortality and a proportionately higher rate of sig nificant sequels Unless enthusiasts for specific types of therapy recognize the strong tendency to spontaneous recovery in poliomyel itis they are apt to find their claims challenged by objective scientists more familiar with the natural history of the disease (Report of Sub committee on Poliomyelitis J A M A 140 534 1949)

11 The second phase or free interval between systemic and men ingeal manifestations may be definitive or relatively inapparent In the most fortunate the free interval is continued indefinitely In the less fortunate systemic manifestations subside then after freedom from dis comfort for several days evidences of meningeal irritation develop In fulminating invasions the free interval is not clearly defined and evidences of meningeal irritation overlap systemic manifestations

12 The importance of recognizing the free interval is reflected in the influence of management during this period on the future course of the disease It is quite possible that continued rest through and following the free period may actually prevent or mitigate meningeal and neurologic manifestations It is al o possible that non specific factors during the free interval such as fatigue anxiety ambulation or surgical intervention (tonsillectomy) may initiate or favor meningeal or neurologic sequels (Horstmann J A M A 142 236 1950)

13 The third phase or stage of meningeal irritation (p 460) may never occur it may overlap the prodromal period or it may be noted after the free interval The course of the meningeal phase also is sub ject to variation in that it may subside without paralysis or it may pro gress to transient or permanent paralyses

14 Excluding abortive infections statistical studies of those who progress to the recognizeable meningeal phase of disease suggest that the fatality rate in poliomyelitis is probably less than 1 per cent and that not more than 2 per cent of survivors suffer significant per manent paralysis These calculations have importance to the therapist who must demonstrate significantly better results before laying claim to specificity of recommended forms of treatment They have impor

9 Except for diagnosis avoid lumbar puncture Do not give intrathecal therapy for reasons elsewhere outlined (p 4409)

10 Despite justifiable reliance on antibiotic therapy do not neglect supportive measures (p 2182) nonspecific medication (p 2183) and oxygen therapy (p 2184) particularly in lobar pneumonia (Fig 496 p 2175)

POLIOMYELITIS

[Acute Anterior Poliomyelitis Infantile Paralysis Heine Medin s Disease]

Principles of Diagnosis and Therapy

1 Poliomyelitis is one of many viral infections re ulting in non suppurative encephalo myelo meningitis (p 442)

2 *The specific virus may be isolated from upper respiratory pas* sages and/or from stools The disease apparently is transmitted from person to person and/or by human fecal contamination So far as is known there is no insect vector both the common house fly and cock roaches having been exonerated

3 Poliomyelitis virus has been grown artificially Three immuno logic subvarieties already have been identified Despite this progress vaccine is not yet available for artificial active immunization

4 Quite likely a single attack of poliomyelitis confers permanent immunity *at least to the individual invading strain* Quite likely also those who appear naturally re istant to the disease have actually developed active immunity from an unrecognized nonparalytic attack of the infection

5 The lesions of poliomyelitis are much more extensive than formerly believed Encephalograms show cerebral changes in *all* patients In fatal cases diffuse encephalitic lesions are demonstrable with destructive processes regularly present in vestibular and cere bellar nuclei Histologic studies suggest that involved nerve cells not destroyed during acute stages of the disease recover spontaneou ly *in* one month or less This demonstration of the healing power of nature requires consideration in any evaluation of therapeutic procedure

6 Clinically the course of infantile paralysis may be divided into I a systemic prodromal phase II a free interval III a period of recog nizable meningeal irritation *and IV a stage of paralysis involving* trunk extremities or structures innervated by bulbar nerves Unevent ful recovery may and usually does follow prodromal and meningeal phases and clinical experiences bear out histopathologic evidences of the powerful tendency to spontaneous recovery exhibited by damaged nerve cells

7 Enunciation of principles of management is made difficult by the protean manifestations of the disease overlap of described phases and the rarity with which the practitioner observes his patient *from the onset of invasion* (p 459)

tainly of no value However aureomycin and chloramphenicol are virucidal and while they have not proven significantly successful in the treatment of poliomyelitis they merit trial for probatory anti infective therapy Neither product has serious toxic potential both can be given orally if they do nothing else they may be counted on to prevent or alleviate secondary infection due to sensitive microbes Combined serum and antibiotic therapy may be carried out without significant discomfort or hazard to the patient admittedly at great and perhaps wasteful expense

21 Preliminary experiences with ACTH are disappointing

Practical Management

Prophylaxis

1 Consider passive immunization by intramuscular injection of 10 to 20 cc of human convalescent serum (Hyland) If this product is not available substitute gamma globulin or human placental extract Of these latter use 20 cc deposited intramuscularly

2 Consider administration of aureomycin or chloramphenicol if for no other rea on than to protect against secondary pulmonary invaders Give large do es since the virus is relatively insensitive at best Approximate an oral dose of 100 mg per kilogram of body weight (3 5 gm for the child weighing 75 lbs)

3 Warn contacts to avoid droplet infection from nose and throat or stool contamination

Immediate Care (Abortive Preparalytic and Nonparalytic Invasions)

1 Unless there are definite evidences of weakness paralysis or excessive toxicity try to care for the child at home Hospitalization requires transportation with resultant excitement fatigue and strange surroundings that may favor progression to meningeal and paralytic phases of the disea e Contrariwise reas urance home comfort easing of tension and prolonged bed re t favor arrest of the di ease without significant sequels

2 Whether in hospital or home institute general measures used for management of the infected patient (p 67)

3 Emphasize the favorable aspects of poliomyelitis in order to allay the panic reaction which accompanies each suspected infection

4 Maintain fluid and metabolic requirements by ordering party foods such as ice cream lollipops candy cold drinks sweetened beverages fruit juices etc

5 Notify health authorities Suggest a round table consultation at this time with pediatrist or internist especially experienced in the management of infantile paralysis together with orthopedist and physiotherapist If necessary seek assistance of the National Founda tion for Infantile Paralysis

tance also to parents whose anxiety may be allayed by the mathematically long odds favoring survival without sequel

15 In only a *statistically small number of patients are significant* paralytic manifestations encountered The fourth or paralytic pha e may run concurrently with the meningeal phase or it may follow it Of non bulbar cases approximately 10 per cent have involvement of arms alone 50 per cent of legs alone and the remainder of both legs and arms with or without involvement of the trunk Mortality in non bulbar poliomyelitis is rare

16 Paralyses usually reach a maximum on or about the fifth day In the majority of instances involved nerve cells recover spontaneously an observation that requires consideration in evaluations of specific therapeutic measures Spontaneous improvement however rarely proceeds after the first month so that improvements noted after this time may be credited to the therapist with a high degree of certainty

17 It is in the bulbar form of poliomyelitis that death is *most likely* to occur In these patient, there is involvement of ninth tenth eleventh and twelfth cranial nerves Clinically bulbar involvement is recognized through regurgitation of fluid through the nose loss of gag reflex *change in the character of the voice the patient developing* a hot potato type of speech weakness of the palate with deviation to the unparalyzed side when the patient says Ah pharyngeal weakness deviation of tongue on protrusion difficulty in swallowing mechanical obstruction to breathing due to paralysis of vocal cords respiratory distress as evidenced by recurrent cyanosis laryngeal stridor and coarse rales excitement and unmanageability causing the patient to resist pharyngeal aspiration elevation of temperature to the highe level of 103° F or more greater toxicity stupor of sufficient degree to make the patient oblivious of the accumulation of secretions in his airway inability to cough effectively pharyngeal pooling of mucus and the presence of leukocytosis when secondary infections occur particularly in the lungs

18 *Specific therapy of poliomyelitis is currently disappointing* As previously stated induction of artificially active immunity is presently not much more than a hope and for available agencies for passive immunization and anti infective effects there are no statistical evidences suggesting great potency

19 A convalescent antipoliomyelitis serum (Hyland) is commercially available The product is obtained from pooled blood of donors recently recovered from the disea e The recommended dose is 10 to 20 cc deposited intramuscularly and repeated daily or every second day for 2 or 3 injections if necessary This homologous product *merits* consideration only for want of something better to do If serum therapy accomplishes nothing else it gives anxious parents the feeling that something is being done without exposing the child to a toxic product

20 Of available antibiotics none has demonstrable specific efficacy in poliomyelitis Sulfonamides streptomycin and penicillin are cer

weakness or faintness) If priscol cannot be accepted orally give sub cutaneous or intramuscular injections of 1 to 2 cc of the commercially available solution (25 mg per cc) at 4 hour intervals

14 As a substitute for sympatholytics cautiously inject cholinergic neostigmine in a probatory dose of 0 5 cc of 1 4000 solution If this amount is ineffectual increase the dose to 1 cc repeated at intervals of four hours if necessary Enthusiastic reports of the innovators (Kabat and Knapp 1943) have not been substantiated by other investigators

15 Other muscle relaxants (intravenous procaine and curare) are too hazardous for use by the practitioner in the home As in tetanus intravenous infusions of 0 1% procaine may jeopardize both respiratory and circulatory systems and intramuscular deposits of Purified Chondro dendron Tomentosum Extract (Intocostrin Squibb) enthusiastically advo cated by Ransohof (J A M A 129 129 1945) are not recommended by Fox (J A M A 131 278 1946) who found no objective improvement in thirty four patients treated with curare and who emphasizes the dangers of its action on respiratory mechanisms (p 4421)

Continuing Care (Favorable Course Free Interval)

1 Continue immediate care for at least five days and preferably a week even if all eems well

2 Maintain complete bed rest for at least another week beyond dis continuance of probatory medication even if child is completely asymptomatic

Continuing Care (Meningeal Phase)

1 If the observed patient progresses to the meningeal phase despite efforts outlined under Immediate Care or the patient is first seen in the meningeal pha e continue or initiate broad steps previously outlined

2 With or without consultants consider or reconsider advisability of serum therapy administration of aureomycin or chloramphenicol prescription of sedatives hypnotics and muscle relaxants and non technical hydrotherapy

3 In addition arrange for non technical physiotherapeutic pro cedures until more expert advice can be obtained With child supine raise foot of bed so that oral secretions gravitate out of mouth and do not collect in pharynx larynx or lower respiratory passages if possible obtain an electrically driven suction drainage apparatus for removal of secretions from oropharynx place a beaver board between spring and mattress to support back put another board at the end of the bed to prevent foot drop place sandbags under shoulders and knees so that latter are held at a 15 degree angle provide ankle pad

4 Try to maintain patient morale by reassurance diversions such as reading and radio listening and by establishment of an air of complete confidence and calm Stress prognostically favorable statistical features emphasized in the discussion of Principles of Diagnosis and Therapy

6 Perform diagnostic lumbar test if diagnosis is in doubt Note clear fluid with cell count ranging be ween 10 and 500 normal sugar and increased protein (p 3736) If fluid is turbid make spread and cultures for pathogens if sugar is ab ent and/or cell count is higher than 500 (Table 194 p 3735) institute search for tubercle bacilli (p 262) Avoid spinal drainage for therapeutic purpose and veto intrathecal instillations of serum or antibiotics for reasons elsewhere outlined in detail (p 4409)

7 Consider immunotherapy by intramuscular deposit of 10 to 20 cc of convalescent serum (Hyland) gamma globulin or placental extract Repeat at 8 12 or 24 hour intervals if necessary

8 Con ider probatory antibiotic therapy with aureomycin or chloramphenicol Give priming and daily maintenance doses approximating 100 mg per kilogram of body weight (3 5 gm for the child weighing 75 lbs) If possible give 2 product every few moments with fruit juice ice cream carbonated beverage soup tea or plain water If stomach is intolerant of either antibiotic substitute the other If neither can be taken orally make a saline solution or su pension warm and instill rectally using a male catheter and a funnel Hold buttocks firmly together to prevent expulsion

9 If child is intolerant of antibiotics both orally and rectally consider intravenous injection of 100 to 500 mg of aureomycin hydrochloride dissolved in the diluent of 0 75% sodium carbonate as supplied by the manufacturer

10 Do not permit overdistention of bladder or rectum Catheterize at 12 to 24 hour intervals if necessary Give a simple rectal flush daily or every second day

11 For sedation and hypnosis employ reas urance reading phonograph records radio listening etc Try to avoid drugs which tend to depress respiration If non pharmacologic efforts fail re ort cautiously to small doses of barbiturates for sedation and hypnosis For the former purpose prescribe 8 to 15 mg (1/8 to 1/4 gr) of phenobarbital at 3 or 4 hour intervals as a sleeping draught prescribe 45 to 90 mg (3/4 to 1 1/2 gr) of sodium seconal swallowed with warm fluid

12 For control of muscle spasm and pain first try hydrotherapy Instruct mother to wring out a blanket in very hot tap water press with a very hot iron at the bedside and apply to involved portions of the body Repeat at 15 minute intervals for one hour out of every three or four Often this improvi ed nontechnical hydrotherapy allays the patient and gives the parent the comfort of making a practical contribution to the recovery of the child

13 If hydrotherapy is unsuccessful in the control of muscle spasm consider supplementation with relaxant drugs (p 4418) For oral use prescribe artane (2 to 5 mg) oranixon (250 mg) priscol (25 mg) and tolserol (250 mg) in tablet form Most reported experience has been with priscol which is adrenolytic and sympatholytic Doses of 25 to 50 mg repeated every four hour are effectual and have negligible toxicity (nausea vomiting and orthostatic hypoten ion producing sensations of

6 Place the tracheotomized patient in an oxygen tent. Maintain con tant professional nursing care most particularly to maintain patency of tracheotomy tube

7 Continue intravenous drip after tracheotomy and introduction of the patient into the oxygen tent. Use the drip for administration of fluid foods (5 to 10% dextrose protein hydrolysate plasma whole blood) antibiotics (aureomycin hydrochloride) and indicated drugs For sedation or hypnosis favor 30 to 90 mg (½ to 1½ gr) of sodium phenobarbital for muscle relaxation if priscol and neostigmine have proven unsatisfactory slowly introduce 200 to 400 cc of 0 1% procaine prepared by di solving 1 gm in 1000 cc of physiologic saline

8 In the pre ence of respiratory difficulty be sure that the airway is clear If the disturbance is not due to obstruction of the respiratory lumen look for acute dilatation of the stomach due to air swallowing If present pa s a Levine tube through nostril and into stomach aspirate air and fluid content with a gla s syringe

9 Have a respirator in readine s long before evidences of severe pulmonary embarra sment are encountered

Convalescence

1 Remember that maximum neurologic damage usually occurs within five days and that spontaneous recovery of nerve cells is terminated after thirty days As soon as meningeal paralytic and bulbar manife tations no longer are the cau e for immediate concern concentrate on restoration and coordination of neuromuscular units left anatomically intact For non technical mu cle re-education provide for passive exercise of joints provided that pain is not produced With subsidence of pain encourage active motion through normal joint range

2 Insist on consultation with physiotherapist and/or orthopedic surgeon for technical a sistance in rehabilitation Do not use splints braces or crutches without approval of specialists

3 Sometime later than one month after onset of paralysis request consultation again with physiotherapist and/or orthopedist Pe a sess degree of neuromuscular recovery Di cuss indicated surgical procedures to minimize disability and provide for maximum rehabilitation

POLLINOSIS

[Pollen Allergy Hay Fever]

Pollen allergies are frequently encountered in clinical practice Therapeutic objectives in the management of these allergic hyper sensitivities include recognition and elimination of ensitizing bacterial or non bacterial agents (p 4176) desensitization or hyposensitization using pollen extracts (p 4191) psychotherapy (p 1316) and palliation and prophylaxis with antihistamines and adrenergens (p 4212)

5 If paralysis does not occur within five days of onset of meningeal phase consider institution of convalescent therapy later outlined.

Continuing Care (Paralytic Phase without Bulbar Involvement)

1 Continue measures previously advocated if child has been under constant observation Inaugurate previous routine if patient has not been seen earlier in the disease

2 Insist on specialist consultation preferably a round table discussion with physiotherapist orthopedist and internist or pediatrist specially trained in poliomyelitis If necessary apply for aid to National Foundation for Infantile Paralysis

3 Consider or re consider use of antibiotics non technical physiotherapy non technical hydrotherapy sedatives hypnotics and muscle relaxants as previously outlined

4 Until specialists arrive supplement hydro and physio therapy by use of electric pad or infra red lamp to affected parts in the interval between attacks and by gentle stroking and passive motion through the normal range of motion several times daily Permit the mother to cooperate for reasons previously described

5 Avoid splints braces and other mechanical supports which may tend to promote atrophy and deformity Use bandages and pillows to protect involved parts

6 As unobtrusively as possible seek evidences of bulbar involvement as previously described If detected proceed according to suggestions that follow immediately if absent carry out measures of convalescence after the critical period of five days

Continuing Care (Bulbar Paralysis)

1 In both meningeal and early paralytic phases look for small signs of bulbar involvement (p 4472) If present institute therapy before subjective manifestations become too marked.

2 Discontinue food fluids and medication by mouth to minimize chances for aspiration pneumonitis

3 Set up an intravenous drip introduce 250 to 500 cc of 5% dextrose in saline add 500 mg aureomycin hydrochloride for intravenous use to prevent secondary infection Consider continuance of intravenous infusion with plasma protein hydrolysate or whole blood if there are definite indications

4 With consultants discuss elective tracheotomy (p 3958) Advocates of this measure have established the following indications for the procedure nasal voice evidences of interference with swallowing mucus pooling in throat and posterior pharynx obstruction or obliteration of free airway increasing anoxemia increasing pulse rate increasing headache and restlessness and pulmonary atelectasis and/or paralysis of vocal cords (West and Dower Am J Med Sci 217 252 1949)

5 If elective tracheotomy is decided as a procedure of choice consider anesthesia with pentothal introduced into the established intravenous drip

The injection schedule outlined above is compressed so that daily injections are administered so long as the patient does not exhibit hypersensitivity

When the sixth injection has been given (0 05 cc of 1 500 solution containing 100 pollen units) time intervals may be increa ed to two or three days provided that symptom relief has been obtained Then at the twelfth injection when 1 50 dilution has been reached intervals may be increased to five or seven days

9 Whether patient is first desensitized by coseasonal or preseasonal schedules make arrangements for *perennial desensitization* Either of the following schedules may be used for this purpose

SCHEDULE FOR PERENNIAL DESENSITIZATION

Day	Dilution	Size of Dose in cc	Noon or Pollen Units
Once each fortnight from October 1 to April 15	1 50	0 2	4 000
May 1	1 50	0 3	6 000
May 15	1 50	0 4	8 000
June 1	1 50	0 5	10 000
June 15	1 50	0 6	12 000
July 1	1 50	0 7	14 000
July 15	1 50	0 8	16 000
August 1	1 50	0 9	18 000
August 15	1 50	1 0	20 000
October 1	1 50	0 2	4 000
Continue fortnightly as above			

ALTERNATE SCHEDULE FOR PERENNIAL DESENSITIZATION

Day	Dilution	Size of Dose in cc	Noon or Pollen Units
Once each fortnight from October 1 to July 15	1 50	0 2	4 000
July 19	1 50	0 3	6 000
July 23	1 50	0 4	8 000
July 27	1 50	0 5	10 000
July 31	1 50	0 6	12 000
August 4	1 50	0 7	14 000
August 8	1 50	0 8	16 000
August 12	1 50	0 9	18 000
August 15	1 50	1 0	20 000
October 1	1 50	0 2	4 000

POLYCYTHEMIA

[See Blood and Blood forming Organs Neoplasms of]

Principles of Diagnosis and Treatment

1 Determine in general date of onset of symptoms (tree pollen from March 15 to May 15 grass pollen from May 1 to July 1 weed pollen from August 1 to October 1)

2 From geographical distribution of grasses and weeds productive of hay fever (Fig 96 p 560) narrow the likely offending pollens o that a minimum number of tests are required

3 Perform scratch tests (p 557 and Fig 94 p 555) using only common pollen antigens under suspicion

4 After termination of tests immediately prescribe antihistamine using any oral product (p 4212) Continue during desensitization and throughout period of pollination

5 From any reliable manufacturer whose product has been approved by the Council on Pharmacy and Chemistry of the American Medical As ociation obtain treatment set for desensitization against pollens to which patient reacts

6 Start pre seasonal treatment if time permits according to following schedule

SCHEDULE OF PRESEASONAL TREATMENT

Dose	Dilution	Size of Dose in cc	Noon or Pollen Units
1	1 5000	0 1	20
2		0 2	40
3		0 3	60
4		0 4	80
5		0 5	100
6	1 500	0 05	100
7		0 1	200
8		0 2	400
9		0 3	600
10		0 4	800
11		0 5	1000
12	1 50	0 05	1000
13		0 1	2000
14		0 2	4000
15		0 3	6000
16		0 4	8000
17		0 5	10 000
18		0 6	12 000
19		0 8	16 000
20		1 0	20 000

Injections given twice weekly

7 If time does not permit completion of schedule for preseasonal treatment as outlined above using two injections a week patient may be given three injections weekly provided there are no serious local or constitutional reactions suggestive of histamine type hypersensitivity

8 If patient arrives during period of pollination *coseasonal therapy* may be attempted cautiously Antihistamine is given in double dosage

disease does streptomycin retain significant current indication Since polymyxin cannot compete with streptomycin in the therapy of tuberculosis it is unlikely that it will find an important niche in the practitioner s armamentarium

Toxicity

On injection polymyxin produces local irritation and immediate histamine type hypersensitivity reactions (p 4167) undoubtedly due to impurities in the mixture More significant are evidences of renal tubular irritation as manifested by albuminuria the presence of leucocytes and casts in the urinary sediment oliguria elevation of blood non protein nitrogen and depression of renal functional tests

Were polymyxin of equal potency against gram negative organisms sensitive alike to it and to aureomycin-chloramphenicol the nephrotoxic potential alone would be sufficient to make the latter preparations of election

PROMIN

Promin possesses the formula sodium p p -diamino-diphenyl sulfone N N di(dextrose sulfonate) The dry powder of promin is off white to light yellow in color It is slightly hygroscopic The 40% aqueous solution used intravenously is a clear light yellow adjusted to *p*H 5 6 to 6 0 In this concentration promin solution is stable indefinitely

Available Products

Promin (Parke Davis) *ampuls* of 5 cc containing 2 gm (40%) For intravenous use

Promin Jelly (Parke Davis) for topical use (5%)

Administration

Oral administration is too toxic for clinical u e and intramuscular injections are painful In consequence promin can only be given intravenously in an initial dose of 1 gm (2 5 cc of 40% solution) increased gradually to 5 gm (12 5 cc of 40% solution) provided that toxic manifestations do not occur earlier (p 4552)

Toxicity

Promin has considerable toxicity principally a destructive action on erythrocytes producing secondary and progressive anemia Less often it cau es leukopenia so that the blood count must be made at frequent intervals to avoid serious difficulties

In addition to major toxic manifestations promin may also cause nausea vomiting headache sneezing and toxicoderms In consequence of the frequency of untoward reactions it is recommended that treatment be discontinued for one day each week and for one or two weeks every four months

POLYMYXIN

Polymyxin an antibiotic that is chemically a polypeptide or mixture of polypeptides is derived from B polymyxa It is very similar to if not identical with aerosporin obtained from B aerosporus (p 4162)

Available Product

Because of its toxicity polymyxin is not commercially available Small supplies are being used for laboratory and clinical investigation

Pharmacology

Polymyxin is obtainable as the water soluble crystalline hydrochloride Its activity is not affected by reactions between pH 2 and 7 It is only slightly affected by blood serum and other mediums at physiologic ranges

Given orally polymyxin is not absorbed and eliminates sensitive fecal organisms Injected intramuscularly in daily doses of 3 to 5 mg per kilogram per day it produces blood levels approximating 0 6 to 1 3 micrograms per 100 cc at the end of twenty four hours Some polymyxin is excreted in urine but none is demonstrable in cerebrospinal fluid

Bacterial Spectrum

Polymyxin was originally introduced to compete with streptomycin It was hoped that the new antibiotic would prove less toxic and less prone to produce resistant bacterial strains (p 4133)

Polymyxin has the advantage over streptomycin in that it is bactericidal whereas the older preparation is bacteriostatic It is equally effective against streptomycin sensitive and streptomycin resistant strains of gram negative bacilli In therapeutic doses it is from 2 to 80 times more potent than streptomycin

Unfortunately present preparations of polymyxin are nephrotoxic as discussed later Furthermore resistant strains to the new antibiotic develop as in the case of streptomycin

The roster of polymyxin sensitive organisms includes E typhosa Salmonellae Shigellae E coli V comma (cholera) H pertussis H influenzae Br melitensis (brucellosis) P plague P tularensis (tularemia) Ps aerogenes (pyocyaneus) and Kl pneumoniae (Friedlander bacillus)

Even granting superiority of polymyxin over streptomycin in the treatment of gram negative bacterial invasions comparison of the bacterial spectrum with that of aureomycin and chloramphenicol (p 4243) reveals the clear superiority of the two latter as compared with more toxic injectable polymyxin

A roster of demonstrably polymyxin resistant organisms includes gram positive cocci gram positive bacilli mycobacteria including tuberculosis and leprosy and fungi

Particularly significant in the list of polymyxin resistant organisms is the presence of M tuberculosis Only in antibiotic treatment of this

2 The diagnosis is established by identification of micro-organism in urine cultures ince there are no characteristic clinical features

3 Urinary sepsis due to Pseudomonas aeruginosa is treated in the manner of tho e produced by A aerogenes (p 4161)

4 The most significant difference in the management of Pseudomonas aeruginosa infections is that chloramphenicol is distinctly the antibiotic of choice

5 Streptomycin and sulfadiazine are second choices to chloram phenicol They may be used as substitutes or supplements

6 For rea ons that are not clear at present Pseudomonas aeruginosa is relatively insensitive to aureomycin

7 As in the instance of urinary infections with A aerogenes anti biotic therapy must be fortified with indicated surgical measures necessary for relief of urinary tract obstruction (p 2264)

PSORIASIS

Principles of Diagnosis and Therapy

1 Psoriasis one of the frequently encountered dermatoses of general practice is easily recognized through its unique appearance (Fig 1001 p 3417)

2 Local measures elsewhere outlined in detail are merely pallia tive (p 3418)

3 Systemic therapy using undecylenic acid cortisone and ACTH gives considerable promise for more satisfactory control of the afflic tion The former product commercially available as sevinon (Schering) is marketed in soft gelatin capsules containing 0 44 gm of undecylenic acid Prescribe 4 capsules 3 times daily for the first week 6 capsules 3 times daily for the econd week 8 to 10 capsules 3 times daily after the second week and continue until there is complete disappear ance of lesions Side effects of oral undecylenic acid therapy include bitter taste mild nausea dyspepsia and frequent bowel movements

4 Perlman (J A M A 139 444 1949) the original proponent of undecylenic acid therapy for psoriasis reports relief of itching and disappearance of lesions in each of seventeen ca es under ob ervation Unfortunately other ob ervers have not encountered such uniformly successful findings

5 Although material has been available only for treatment of a very few patients injections of corti one and ACTH appear to have com plete specificity in psoriasis Should these preliminary results be sub stantiated psoriasis will be added to the growing list of allergic hypersensitivities (p 4167)

PROMIZOLE

Promizole (4 2 diaminophenyl 5 thiazolyl sulfone) is an isostere of 4 4 diamino diphenyl sulfone having a 2 amino thiazolyl radical replacing one amino phenyl group of the parent sulfone The dry powder is off white color and stable It is soluble in water to the extent of 30 to 40 mg per 100 cc at 30° C

Available Products

Promizole Tablets 0 5 gm (Parke Davis)

Administration

Promizole is administered orally in tablet form The initial dose is 0 5 gm given three times daily at meal time gradually increased to an optimal dose of 6 to 8 gm daily Rest periods are given as in diasone therapy (p 4552)

Toxicology

Toxic manifestations are rare and usually mild When they occur they are similar to those of other sulfones

PROTEUS VULGARIS INFECTIONS

Principles of Diagnosis and Therapy

1 Proteus vulgaris is capable of producing both urinary and meningeal infections

2 Invasions are managed in the manner of those caused by A aerogenes (p 4161)

3 Chloramphenicol is the antibiotic of choice with streptomycin and sulfonamide held in reserve for substitution or supplementation if necessary

4 For reasons that are presently unknown aureomycin is relatively ineffectual

5 As in the case of A aerogenes urinary infections antibiotic therapy must be accompanied by indicated surgical procedures to eliminate urinary tract obstruction (p 2264)

6 In Proteus vulgaris meningitis combined antibiotic therapy (chloramphenicol streptomycin sulfadiazine) must be supplemented with necessary surgical procedures such as ligation of internal jugular vein

PSEUDOMONAS AERUGINOSA (B PYOCYANEUS) INFECTIONS

Principles of Diagnosis and Therapy

1 Pseudomonas aeruginosa most frequently causes urinary tract infections (p 2334)

Practical Management

1 Institute non specific treatment of the infected patient (p 67–73)

2 Inaugurate specific anti infective therapy with aureomycin or chloramphenicol Give a priming dose of 50 mg per kilogram of body weight (3 5 gm for the average adult weighing 150 lbs) Accomplish this by requesting the patient to swallow 2 products every few minutes until the entire loading dose has been administered.

3 Beginning four hours after completion of the priming dose start maintenance doses of 2 products (500 mg) every four or six hours depending on patient response and intensity of infection

4 If stomach is intolerant to either antibiotic substitute the other Should gastric irritation be produced by ingestion of both products pass a duodenal tube and give the contents of either or both in solution or suspension transduodenally

QUINACRINE U S.P

Quinacrine is chemically 3-chloro-7 methoxy 9(1 methyl-4-diethyla mino lentylamino) acridine hydrochloride It is a potent but toxic antimalarial made virtually obsolete by newer and less toxic prepara tions especially chloroquine (p 4283) and chlorguanide (p 4281) It is the anthelmintic of choice in teniasis

Available Products

Atabrine Dihydrochloride (Winthrop) Tablets of 50 and 100 mg Ampuls containing 200 mg with 10 cc ampuls of sterile distilled water for use as diluent

Pharmacology Therapeutics and Toxicity

See p 519

The status of quinacrine has been altered remarkably by introduction of newer antimalarials Where the efficacy of quinacrine approached that of chloroquine and chlorguanide as in the suppression of malaria the negligible toxicity and non pigmentary properties of the newer products throws the balance clearly in their favor

In severe infections quinacrine may be injected intramuscularly in the dose of 0 4 gm in 20 cc of sterile distilled water using both but tocks As soon as the patient is able to swallow one of the newer prod ucts is substituted

QUININE ETHYL CARBONATE N.F

Quinine ethyl carbonate is a white odorless tasteless powder con taining approximately 82% of Quinine (p 4486) Its chemical formula is $C_2H_5O\ CO\ OC_{20}H_{23}N_2O$

PSYCHOGENIC ALLERGY

Psychogenic allergies occur very frequently (p 552) Usually they *are in the nature of attacks of urticaria angioneurotic edema* bronchospasm and neurodermatitis Therapeutic objectives include psychotherapy (p 1316) and palliation and prophylaxis using adrenergens and antihistamines (p 4212)

Initial efforts at psychotherapy are limited to non technical methods (p 1316) particularly striving to establish, for the patient the relationship between eruption and emotional affect With persistence of symptoms of sufficient severity consider reference for formal psychotherapy particularly by analytic technics (p 1328)

Q FEVER

[Nine Mile Fever]

Principles of Diagnosis and Therapy

1 Q fever is a specific rickettsemia caused by Rickettsia burneti Q fever is undoubtedly more common in the United States than is generally believed Many individuals particularly in the Southwest have had the disease without being aware of its presence as attested by antibodies found in analyses of five thousand serum specimens

2 Cattle undoubtedly account for the transmission of Q fever although the manner in which human beings become infected is unknown There is grave suspicion of an intermediary insect vector

3 Clinical manifestations include elevation of temperature headache muscle aches chilliness and respiratory symptoms *These last* may be in the upper passages causing sneezing nasal obstruction and sore throat but more often they are in the nature of a pneumonitis resembling the lesion of a virus pneumonitis (p 4636) Cough is generally dry and non productive Later in the disease dulness and rales appear but there are rarely signs of frank consolidation Neither spleen nor lymph nodes enlarge The temperature generally persists untreated for five to fourteen days and usually exceeds 102 F (p 382)

4 Radiographs usually show a pulmonary lesion with an infiltration of uniform ground glass density The shadows are usually circumscribed in peripheral portions of the lung This appearance is in contrast with that of virus pneumonitis where the lesion is usually feathery and spreads fanwise from hilus to periphery

5 The diagnosis of Q fever is made definitively by isolation of rickettsia from blood during acute stages of the disease and by increase in titer of specific antibodies during convalescence Q fever is differentiated from virus pneumonitis in that cold hemagglutinins are not demonstrable and from other rickettsemias in that there is no change in the Weil Felix reaction

RABIES

[Hydrophobia Lyssa Derriengue]

Principles of Diagnosis and Therapy

1 Rabies is one of many neurotropic virus diseases producing non suppurative encephalomyelomeningitis (p 442)

2 For the most part rabies is transmitted to humans through the bite of the dog but other animals also are reservoirs of infection (p 439)

3 Large cale prophylaxis of rabies could be accompli hed if all licensed animals were subjected to compulsory immunization and muzzling and if all non licensed ownerless unmuzzled animals were destroyed Accomplishment of this goal is obstructed by a large and highly vocal group of dog fanciers who tend to resist any effort to interfere with the dog population While such people may reject a program based on protection of human beings they can scarcely fail to accept one designed for the protection of the dog

4 For active immunization against rabies several officially accept able vaccines are commercially available for use in human beings as well as dogs

5 Rabies vaccines are uncontaminated suspensions of attenuated diluted dried or dead fixed virus of rabies Virus is obtained from central nervous tissues of animals suffering from fixed virus rabies infection

The National Institute of Health of the United States Public Health Service exercises rigid controls over rabies vaccines The Council on Pharmacy and Chemistry of the American Medical Association recog nizes vaccines prepared by the following methods

RABIES VACCINES

Method	Preparation	Administration	Manufacturer
Pasteur	One fifth inch of dried cord, emulsified in 0 6 cc of 60% glycerine containing 0 3% tricre sol	Get three sets each of seven doses Dilute dried cord with 2 5 cc of sterile saline at time of injection Inject sub cutaneously once daily for twenty one days	Un States Public Health Service
Harris	Bra ns and cords ground to paste frozen with CO_2 snow and rapidly dried and stored in vacuo in cold	Give contents of one vial in increasing unitage daily for ten to fourteen days	Dr D L Harris Labora tory or Eli Lilly
Semple	Brains or cords tritur ated with isotonic sal ne conta ning 1% phenol stra ned incubated di luted with saline to strength and put up in vials containing single daily dose	Give contents of vial subcutaneously daily for seven to twenty eight days	Cutter Lederle Medi cal Arts Laboratory National Drug Co Sharp & Dohme Squibb United States Standard Products Co or Wyeth

Available Products

Euquinine (Mallinckrodt Merck) Powder

Therapeutics

For use as antipyretic and antimalarial in capsule doses of 0 3 gm (5 gr) three times daily Euquinine has the advantage over crude quinine in that it is tasteless Toxic symptoms are reputedly less common and less severe

Toxicology

See Cinchonism (p 518)

QUININE N F

Quinine formerly the antipyretic and analgesic of choice has yielded to less toxic and equally efficacious preparations such as acetyl salicylic acid (p 3832) formerly the sole antimalarial of proven efficacy it has been superseded for the most part first by quinacrine (atabrine) and pamaquine (plasmochin) and more recently by chloroquine (aralen) and chlorguanide (paludrine)

Whereas quinine toxicity has resulted in a virtual total eclipse in the symptomatic management of pains and fever quinine salts still have a place in the treatment of malaria The residual indications appear to be

1 rapid defervescence of acute attacks
2 intravenous injection in the comatose patient
3 combined with pentaquine or isopentaquine for treatment of relapsing vivax infections (p 4398)

Available Products

Quinine Bisulfate U S P
Quinine Dihydrochloride U S P
Quinine Ethylcarbonate (Euquinine) *U S P*
Quinine Hydrochloride U S P
Quinine Sulfate U S P

Of these quinine sulfate is most commonly used in capsules of 60 120 200 250 and 300 mg For injectable use the soluble dihydrochloride is prepared by dissolving 0 6 gm in 300 cc of sterile physiologic saline

Pharmacology

See p 516

Toxicity

See Cinchonism p 518

By comparison vaccine gave no protection whatsoever and combined antiserum and vaccine treatment did not enhance the beneficial effect of antiserum given alone In a small group of human cases antiserum concentrate was administered intramuscularly in doses of 1 to 1 5 cc per kilogram of body weight The clinicians involved did not wish to hazard human lives by omitting vaccine treatment entirely so that each of these patients was given additionally a 7 to 21 day course of vaccine To date none of the twenty patients has shown any signs of rabies Until there is further information physicians who see rabies may communicate with the Lederle laboratories to obtain serum Koprowski advises that antiserum be employed in conjunction with vaccine in all exposures at least for the present However a course of seven injections may be considered as sufficient in conjunction with anti erum in place of the 14 or 21 day course

10 Finally there are evidences that aureomycin and chloramphenicol may prove virucidal for the rabies organism If preliminary observations are substantiated it may be that both rabies vaccine and hyperimmune serum will be rendered obsolete

Practical Management

1 The animal that inflicted the wound should not be destroyed Notify local health or police authorities to apprehend the dog for observation It is unnecessary to induce active immunization in the human unless the dog shows prior clinical evidences of hydrophobia

2 Though all authorities agree that every effort should be made to remove virus from the portal of entry there is conflicting opinion concerning the actual technic of wound treatment Thus Johnson recommends that the wound be thoroughly washed under local anesthesia with 20% soap solution In his opinion this is undoubtedly the best method of removing or inactivating virus

3 In contrast to Johnson s opinion the time honored technic for treatment of dog bite requires cauterization with concentrated nitric acid (p 3969)

4 The physician who treats an occasional wound inflicted by a potentially rabid animal cannot omit cauterization with nitric acid despite the consequences of greater scar formation particularly in more serious bites of the face Wounds about the head are 16 times as lethal as those of the hands and arms and 80 times as dangerous as those of legs It is all very well for the experienced expert with institutional backing to rely wholly on a washing with concentrated soap solution but the i olated practitioner cannot assume this responsibility

5 If the dog cannot be apprehended or if he gives evidences of clinical hydrophobia antirabies therapy must be inaugurated For this purpose obtain any commercially available Council approved rabies vaccine Carry out injections according to instructions provided by the manufacturer Peassure patient and family that only one human of each 1000 to 2000 persons suffering dog bite develops rabies Sedate with 15 to 30 mg phenobarbital every three to four hours and prescribe hypnotic at bedtime

RABIES VACCINES *(Continued)*

Method	Preparation	Administration	Manufacturer
Chloroform Killed	Vaccine prepared as by Semple technic but with *substitution* of chloro form for phenol	Inject 0 5 cc daily for seven to twenty-eight days	Wyeth
Ultraviolet Irradiation Killed	Tissue suspension in a continuously flowing thin stream exposed to germicidal rays of an *ultraviolet lamp* and preserved with 1 10 000 sodium ethylmercurthi osalicylate	Inject 1 cc subcutane ously daily for fourteen to twenty-one days	Pitman Moore

6 Immunization with rabies vaccine may produce a postvaccinal encephalopathy (p 4307) Some claim that postvaccinal encephalo pathy has caused more deaths than rabies itself This hazard has been attributed to introduction of a rabies like virus in the vaccine such as occurred when the virus of homologous serum jaundice contaminated yellow fever vaccine (p 4358) To obviate this complication ultra violet irradiated vaccine is available

A second and more likely explanation of postvaccinal encephalo pathy is production of allergic hypersensitivity (p 4169) Supporting the latter view is a recent experience in which postvaccinal encephalo pathy yielded to treatment with antihistamine In addition there has *been produced a rabies vaccine freed by methods of extraction from* those factors productive of allergic hypersensitivity

7 The relationship of rabies to postvaccinal encephalopathy has been the subject of study by Pait and Pearson in Los Angeles County (Am J of Pub Health 39 875 1949) In the experiences of these *writers the chances of acquiring rabies from a known dog* bite approxi mate 1 in 1400 to 1 in 2100 In Los Angeles County a single human case of rabies is annually encountered Nevertheless eight hundred persons are given rabies vaccine each year Of over five thousand individuals subjected to rabies vaccination nine developed postvaccinal encephalopathy with one death (approximately 1 in 600) These figures confirm the opinion of Sellers that postvaccinal encephalopathy has caused more death than rabies itself

8 While the hazards of postvaccinal encephalopathy are thus stressed antivivisectionists and others who agitate to prevent medical progress must not take these figures out of text Without available vaccine both animal and human populations might well suffer serious ravages of the disease

9 In addition to rabies vaccine there have been made available hyperimmune rabbit and sheep serums (Koprowski) Concentrates of these products retaining only gamma globulin fractions are currently under investigation for passive immunization of *animals and humans*

In experiments with hamsters a single injection of antiserum given twenty four hours after exposure proved protecti e as against 100 per cent mortality among the untreated

By comparison vaccine gave no protection whatsoever and combined antiserum and vaccine treatment did not enhance the beneficial effect of antiserum given alone In a small group of human cases antiserum concentrate was administered intramuscularly in doses of 1 to 1 5 cc per kilogram of body weight The clinicians involved did not wish to hazard human lives by omitting vaccine treatment entirely so that each of these patients was given additionally a 7 to 21 day course of vaccine To date none of the twenty patients has shown any signs of rabies Until there is further information physicians who ee rabies may communicate with the Lederle laboratories to obtain serum Koprowski advises that antiserum be employed in conjunction with vaccine in all exposures at least for the present However a course of seven injections may be considered as sufficient in conjunction with anti erum in place of the 14 or 21 day course

10 Finally there are evidences that aureomycin and chloramphenicol may prove virucidal for the rabies organism If preliminary ob ervations are substantiated it may be that both rabies vaccine and hyperimmune serum will be rendered obsolete

Practical Management

1 The animal that inflicted the wound should not be destroyed Notify local health or police authorities to apprehend the dog for observation It is unnecessary to induce active immunization in the human unless the dog shows prior clinical evidences of hydrophobia

2 Though all authorities agree that every effort should be made to remove virus from the portal of entry there is conflicting opinion concerning the actual technic of wound treatment Thus Johnson recommends that the wound be thoroughly washed under local anesthesia with 20% soap solution In his opinion this is undoubtedly the best method of removing or inactivating virus

3 In contrast to Johnson s opinion the time honored technic for treatment of dog bite requires cauterization with concentrated nitric acid (p 3969)

4 The physician who treats an occasional wound inflicted by a potentially rabid animal cannot omit cauterization with nitric acid despite the consequences of greater scar formation particularly in more serious bites of the face Wounds about the head are 16 times as lethal as those of the hands and arms and 80 times as dangerous as those of legs It is all very well for the experienced expert with institutional backing to rely wholly on a washing with concentrated oap solution but the isolated practitioner cannot assume this responsibility

5 If the dog cannot be apprehended or if he gives evidences of clinical hydrophobia antirabies therapy must be inaugurated For this purpose obtain any commercially available Council approved rabies vaccine Carry out injections according to instructions provided by the manufacturer Rea sure patient and family that only one human of each 1000 to 2000 persons suffering dog bite develops rabies Sedate with 15 to 30 mg phenobarbital every three to four hours and prescribe hypnotic at bedtime

6 Since it is generally conceded that Pasteur treatment is futile for individuals so severely bitten by rabid animals that the incubation period is shorter than thirty days administer hyperimmune serum to those patients who exhibit clinical symptoms less than a month after the bite Since hyperimmune serum concentrate is not yet commercially available contact Koprowski at the Lederle Laboratories in Pearl River New York for material and instructions

7 Pending more complete reports administer probatory anti infective therapy with aureomycin or chloramphenicol Give a prim ing dose approximating 100 mg per kilogram of body weight (7 gm for the average adult weighing 150 pounds) Suggest that 2 products be swallowed every few minutes with an abundant amount of water milk fruit juice ice cream tea or bouillon to avoid gastric irritation Four hours after the loading dose has been ingested start daily main tenance doses using a quantity equal to the priming dose divided into 4 equal portions given at 6 hour intervals

8 Whether the patient i given vaccine serum antibiotic alone or in combination institute prophylactic antihistaminic therapy using daily doses of 200 mg of pyribenzamine or benadryl concurrently with specific therapy and for at least two weeks following la t exposure to therapeutic antigen

9 For control of neuromuscular symptoms adopt measures employed in tetanus (p 4566)

RAT BITE FEVER

[Sodoku Haverhill Fever]

General Principles of Diagnosis and Therapy

1 Rats may infect man with Spirillum minus or Streptobacillus moniliformis (p 363)

2 Disease may be tran mitted by rat bite (Fig 55 p 362) or by con tamination of food supplies particularly milk

3 Spirillum minus is sensitive both to aureomycin and penicillin streptobacillus is penicillin resistant but streptomycin sensitive

4 Because of the severity of the disease and its untreated fatality rate approximating 10 per cent combined antibiotic therapy is warranted

Practical Management

1 Deposit intramuscularly 600 000 units of procaine penicillin G in aqueous suspension and 2 gm of streptomycin

2 Begin prophylactic antihistamine therapy using daily oral do es of 200 mg of pyribenzamine or benadryl

3 Continue with daily maintenance doses of 600 000 unit of pro caine penicillin G in aqueous suspension and 1 to 1 5 gm strepto mycin Give latter in 2 or 3 divided doses

4 If a favorable re ponse has not been obtained within forty eight

hours give additionally an oral priming dose of aureomycin approximating 50 mg per kilogram of body weight (3 5 gm for the average adult weighing 150 pounds) To prevent gastric irritation give 2 products every few moments with large quantities of water milk tea ice cream or cream cheese

5 If oral aureomycin is not tolerated inject 100 mg intravenously in diluent supplied by manufacturer

6 If response is unsatisfactory set up intravenous drip Deliver alternately 250 000 units of crystalline potassium penicillin G 100 mg of aureomycin hydrochloride and 0 5 gm streptomycin every 6 8 or 12 hours During intervals maintain drip with physiologic saline 5% dextrose or plasma as indicated

RELAPSING FEVER

[Famine Fever Garapata Disease Kimputu Mianeh Fever Ruckfall Typhus Spirillum Fever]

Principles of Diagnosis and Therapy

1 Relapsing fevers (p 357) are treponematoses produced by a variety of Borrelia (Fig 53 p 358) and transmitted to man by lice or ticks

2 Characteristic of the infection is the temperature chart which reveals initial febrile periods of four to ten days free intervals of seven to fourteen days and a series of recurrences each of which is shorter than the previous episode Eventually the patient develops a permanent immunity and is cured

3 The diagnosis is established by demonstrating Borrelia in blood by Wright s stain darkfield examination or intraperitoneal animal injection

4 Louse borne relapsing fever may be prevented by use of insecticides and insect repellents notably DDT (p 4373) Tick borne epidemics are less easily controlled since the vector is insusceptible to most insecticides including DDT Tick borne attacks are prevented by avoiding tick bites and by removing ticks as soon as they have attacked but before they have fed

5 The various Borrelia provocative of relapsing fever are penicillin sensitive

6 Relapsing fever responds to penicillin Of fifty two patients with the louse borne variety treated by Ingraham and Lapenta all responded to 25 000 units given intramuscularly every three hours to total 1 million units There were no relap es whereas the relapse rate in untreated controls was 87 per cent Improvements in penicillin therapy should afford equally specific results from single deposits of 300 000 to 600 000 units of procaine penicillin G in aqueous suspension or sesame oil with or without 2% aluminum monostearate given intramuscularly daily for perhaps a week

7 The use of arsenicals has become obsolete due to the high efficacy of penicillin and its low toxicity

RESPIRATORY SYSTEM NEOPLASMS OF

Neoplasms of the respiratory passages are being encountered much more often than previously Whether this is due to more accurate diagnostic acumen or an actual increase in the incidence of bronchopulmonary growth is of academic importance Far from academic however is the fact that thoracic surgery has been so perfected that the expertly trained surgeon enters the pleural cavity with slightly less risk than is associated with laparotomy

These considerations spur the practitioner to make the early diagnosis of asymptomatic malignancy for purposes of rapid reference to consulting thoracic surgeon

NEOPLASMS OF UPPER RESPIRATORY PASSAGES

Practical Management

1 During routine examination observe nose and nasopharynx for evidences of ulceration or neoplasm (Fig 473 p 2069)

2 If there is a positive finding refer patient to specialist for biopsy

3 Obtain blood for serologic tests for malignancy (p 4431)

4 With a malignancy or precancerosis discuss with the consultant possible excision or roentgen therapy

NEOPLASMS OF LARYNX

Practical Management

1 Entertain a high index of suspicion with the complaint of continued hoarseness (p 2160) or sore throat (p 2071) especially if there is no antecedent history or evidence of infection and the patient is beyond the age of 35

2 By mirror laryngoscopy look for evidences of neoplasm or ulceration (Figs 474 and 475 p 2073)

3 Obtain blood for serologic tests of malignancy (p 4431) and syphilis

4 Unless mirror laryngoscopy is completely satisfactory refer patient to consulting laryngologist

5 Obtain x ray of chest in usual postero anterior position Also make right and left lateral obliques focussed over larynx for observation of airway

6 Request consulting laryngologist to obtain specimens for surface biopsy or section

7 If there is suspicion of malignancy or actual proof of cancer discuss therapy by laryngectomy and/or irradiation

NEOPLASMS OF BRONCHI LUNGS PLEURA AND MEDIASTINUM

Practical Management

1 Poutine fluoroscopy of the chest makes it possible to recognize asymptomatic neoplasms of bronchi pleurae and lungs The com pleat practitioner overlooks no opportunity to place his patient behind the creen and investigate localized areas of radio-opacity

2 Fluoroscopic and radiographic examinations of the chest are mandatory in the presence of cough (p 2050) continued expectora tion pain in the chest (p 2080) mediastinal displacement (p 2084) and hemoptysis (p 2058)

3 With any broncho pulmonary involvement obtain sputum for routine bacterial examination guinea pig injection and cytodiagnosis by Papanicolaou method

4 Get chest x rays in various positions and compare findings with radiographs of proven neoplasms (Figs 478 and 479 p 2079 Fig 480 p 2082 Figs 482 and 483 p 2083)

5 Get blood for serodiagnosis of malignancy (p 4431)

6 If pleural fluid is obtainable perform thoracentesis and send material to clinical pathologist for cytodiagnosis by Papanicolaou method

7 In the pre ence of any suspicious circumstance order bronchos copy (Fig 476 p 2074 and Fig 477 p 2076)

8 Request bronchoscopist to obtain surface spreads or a tissue pecimen for cytodiagnosis

9 If an intrathoracic tumor is inacce sible to usual examination consider exploratory thoracotomy

10 In the presence of positive findings refer patient to thoracic surgeon for radical removal of neoplasm

RHEUMATIC FEVER

Principles of Diagnosis and Therapy

1 In the light of current knowledge rheumatic fever requires redefinition It may be classified as a complex in which manifestations of bacterial allergy are superimposed on those due to bacterial infec tion The pathogen in most if not all instances is the hemolytic strep tococcus (Lancefield Group A) presenting symptoms and signs are due to microbic invasion and to hypersensitivity manifestations result ing from perverse responses of host tissues to alien bacterial protein (p 4171)

2 For guidance in the management of the patient with rheumatic fever four pha es of the complex require identification despite the fact that they often overlap particularly when recurrences are pro voked by fresh hemolytic streptococcal invasions or by non specific excitants such as fatigue strain cold or trauma (Waksman)

3 In Phase I of rheumatic fever the tissues of a constitutionally

predisposed host are invaded by hemolytic streptococci (p 187) The clinical manifestations of this infection may be so mild as to pass unnoticed they may be vague giving no hint of their potentially dire consequences they may simulate ordinary upper respiratory infections and masquerade as the common cold or an influenza they may be more precise and localize as attacks of nasopharyngitis tonsillitis or pneumonitis they may be more generalized accompanied by systemic symptoms and a generalized eruption such as the scarlatiniform rash of scarlet fever (p 171)

4 Therapeutic objectives in the management of Phase I are elimination of offending bacteria prevention of allergic hypersensitivity manifestations and avoidance of further exposure of the hypersensitive patient to therapeutic allergens The latter category unfortunately includes salicylates iodides gold sulfonamides normal and convalescent serums plasma and human blood

5 Whatever the symptoms and signs of the initial phase of rheumatic fever and irrespective of the degree of their severity potentially allergenic bacterial protein enters the tissues of the hypersensitive host inaugurating the second phase of the complex Phase II ominously silent so far as clinical manifestations are concerned corresponds to the incubation period of other tuberculin type hypersensitivities (p 4169) Objective evidence of immunologic changes that occur during Phase II first noted by Coburn is the phase reaction consisting of the formation of a heavy flocculent precipitate when serum of a patient in Phase II is mixed with serum of a patient in Phase III While no claim for specificity or universality is made for the phase reaction its present importance is that of an indication of the profound immunologic alterations that characterize rheumatic fever In addition to the phase reaction serums of infected patients possess high titers of antistreptolysin O and antihyaluronidase Presumably these immune bodies develop in response to exotoxins secreted by hemolytic streptococci streptolysin lakes erythrocytes while hyaluronidase liquefies connective tissue

6 Therapeutic goals in Phase II of the rheumatic fever complex are entirely prophylactic The practitioner attempts to eliminate hemolytic streptococci through use of hypo allergenic antibiotics to prevent hypersensitivity reactions with antihistamines currently available and with hormones possessing adrenocorticotropic or adrenocortical activity when these more potent agencies are in greater supply and to extirpate or drain foci harboring hemolytic streptococci particularly in upper respiratory passages and most especially in accessory nasal sinuses and tonsils

7 Phase III is characterized by proliferative and exudative abacterial lesions involving the entire mesenchymal apparatus (Collagen Diseases p 4290) These may be observed in endocardium (Fig 21 B p 188) myocardium (Fig 21 A p 188) pericardium pleura lungs subcutaneous tissues joints periarticular structures brain and skin (p 190) During Phase III hemolytic streptococci may or may not be demonstrable in upper respiratory areas but blood cultures are always

sterile leukocytes are increased erythrocytes decreased and erythrocyte sedimentation rate accelerated There is usually an aseptic pyrexia (p 23) which may be relative or absolute (p 3485)

8 Phase III of the rheumatic fever complex is uninfluenced by treatment with antistreptococcal drugs but its manifestations are miraculously dissipated by cortisone or ACTH and perhaps by other products possessing adrenocorticotropic or adrenocortical activity (Hench et al Proc of the Staff Meet of the Mayo Clin 24 277 1949)

9 Phase IV of the rheumatic fever complex is characterized pathologically by scarring usually noted most consistently in myocardium and endocardium These cicatricial lesions are uninfluenced by antistreptococcal preparations by antihistamines or by the potent newer products They provide sites of diminished resistance for later invasion by less virulent streptococci usually of the viridans variety resulting in subacute bacterial endocarditis (p 1021) These scarrings also produce mechanical circulatory difficulties with diminution in cardiac reserve and eventual production of backward failure (p 941)

10 Therapeutic goals in the management of Phase IV of the rheumatic fever complex are identical with those of Phase II Additionally efforts are directed at prevention and relief of the consequences of congestive failure

11 For active therapy of various phases of the rheumatic fever complex the practitioner has at his disposal antirheumatics (salicylates iodides and gold) sulfonamides antibiotics particularly penicillin aureomycin and chloramphenicol antihistamines and products capable of stimulating or simulating adrenal cortical activity

12 Although salicylates are still regarded by some authorities as possessing specificity in the treatment of rheumatic fever actually they appear to have only symptomatic value in Phase III where they are demonstrably antipyretic and analgesic and where they visibly reduce swelling and redness of inflamed joints They do not prevent development of vascular and myocardial lesions of the anaphylactic hypersensitive type though they may lessen pericardial endocardial and valvular manifestations Those who remain impressed with the virtues of salicylates explain their alleged antirheumatic propensities on possible interference with the metabolism of connective tissue through conjugation with glucuronic acid and or glycin and through interference with the water binding properties of mucopolysaccharides (Reagan and Myers)

13 Against the use of salicylates is the demonstration that the drug is capable of being a hyperallergen both experimentally and clinically (p 4178) Stated otherwise the therapeutic agent of itself actually may cause a syndrome identical with that which it is supposed to cure On the basis of these observations we are included among those who currently withhold salicylates in rheumatic fever Even in Phase III we favor control of fever by hydrotherapy of pain by new morphine substitutes devoid of significant side reactions (adanon demerol dolophine isonipecaine meperidine and methadone) and we prescribe antihistamines which simulate salicylates in their pre

vention of pericardial endocardial and valvular lesions at least in the experimental animal

14 The case for the antirheumatic specificity of iodides and gold is much weaker than that for salicylate In point of fact few clinicians today prescribe either of these remedies in rheumatic fever although chrysotherapy still has its advocates in the management of rheumatoid arthritis (p 4502) Neither iodide nor gold provides demonstrable symptomatic relief even in Phase III each is capable of producing tuberculin type hypersensitivity manifestations and additionally gold has intrinsic toxicity particularly objectionable in the management of afflicted youngsters (p 4346)

15 Sulfonamides are definitely streptococcicidal As such they have therapeutic value in the management of Phases I and II However they do not prevent hypersensitivity manifestations and indeed appear *to influence unfavorably the third phase of the rheumatic syndrome* They possess inherent toxicity and additionally have proven their hazardous potential in the production of tuberculin type hypersensitivity reactions closely simulating those that follow introduction of hemolytic streptococci in patients predisposed to rheumatic fever (p 4173)

16 We are among those who oppose the use of sulfonamide in the prevention or treatment of rheumatic fever At least equally effective streptococcicidal effects are obtained from penicillin aureomycin and chloramphenicol each of which is relatively non toxic and hypo allergenic

17 We favor the use of penicillin as the antibiotic of choice in the treatment of the rheumatic fever complex Penicillin is powerfully streptococcicidal whether given orally or parenterally it may produce an occasional histamine type hypersensitivity reaction but the more dangerous tuberculin type phenomena have not yet been reported in striking contrast to observations made on salicylates sulfonamide iodide and gold

18 Penicillin for all of its streptococcicidal potential does not prevent exudative and proliferative hypersensitivity manifestations Hence it is of limited value in Phases III and IV other than for suppression of recurrent invasion by offending microbes

19 The unusual patient who cannot be given penicillin due to hypersensitivity manifestations may be treated by substitution of aureomycin or chloramphenicol Unlike sulfonamide these newer antibiotics are not hyperallergenic They have accounted for an occasional histamine type hypersensitivity reaction but like penicillin no tuberculin type lesions have been observed following their experimental or clinical use

20 We favor prescription of antihistamines in all phases of the rheumatic fever complex They prevent hypersensitivity manifestations due to invading microbe or therapeutically introduced antibiotic Experimentally at least one of the group (benadryl) apparently lessens the development of pericardial endocardial and valvular lesions in the manner of sodium salicylate Benadryl does not prevent vascular

and myocardial lesions of the anaphylactic hypersensitive type nor has it any effect on exudative or proliferative lesions observed in the third phase of the rheumatic fever complex

21 Cortisone and ACTH in Phase III of the rheumatic fever complex cause rapid disappearance of fever tachycardia polyarthritis and abnormalities in the electrocardiogram (Hench et al loc cit) However the newly developed products are not streptococcicidal and hence cannot be used as substitutes for antibiotics Discontinuance of hormonal therapy is followed by exacerbation of previously ameliorated manifestations suggesting that the response is purely symptomatic

22 Justifiable enthusiasm for newly developed antibiotics and hormones must not overshadow the importance of inaugurating or continuing established measures of non specific therapy in the care of the patient with rheumatic fever (pp 194–199) It is still necessary to insist on prolonged bed rest an adequate diet psychotherapy removal or drainage of infected foci and judicial consideration of decisions that concern interval surgery marriage and pregnancy (p 198–199)

Practical Management

Prophylaxis

1 Regard as potential sufferers from rheumatic fever all children with family or personal histories of overt attacks those with objective manifestations of a previous attack (valvular defect) and those with otherwise inexplicable subjective or objective evidences of ill health (failure to gain weight fevers of unknown origin recurrent respiratory infections anemia tachycardia etc)

2 Regard as possible Phase I of rheumatic fever all respiratory infections and definitively established hemolytic streptococcal invasions such as septic sore throat scarlet fever and erysipelas (pp 167–186) Be especially wary when faced with the combination of potential Phase I invasion occurring in the potentially rheumatic youngster

3 Protect the potentially rheumatic child by insistence on general measures of hygiene including a full diet adequate housing facilities provision for central heating and sufficient rest throughout the school year

4 Correct anemia by diet and/or by prescription of hematinics if necessary (p 3897)

5 Insist on triple immunization against diphtheria tetanus and pertussis (p 4365) Episodes of rheumatic fever may be precipitated by other intercurrent infections

6 Recommend summer vacations in the country for the city child Especially support summer camps for underprivileged who suffer from rheumatic fever

7 Favor outdoor exercise but restrict competitive sport if the latter is productive of excessive strain or fatigue

8 Search for foci harboring hemolytic streptococci Favor intranasal surgery for drainage of blocked accessory nasal sinuses and adenoidectomy with or without tonsillectomy if indicated

9 Despite these precautions try to avoid seeding an anxiety neurosis

10 Provide for desensitization if the youngster exhibits allergic manifestations to allergens other than hemolytic streptococcus Particularly protect against drug food and pollen syndromes (p 4477)

11 Throughout the school year rid the upper respiratory passages of hemolytic streptococci by prescription of 250 000 units of crystalline potassium penicillin G in tablet form after each meal and at bed time for the first seven days of each month Repeat during the month if there is exposure to respiratory infection By this step alone recurrences of rheumatic fever were completely eliminated in susceptible children as against an attack rate of 11 to 19 per cent in control groups

12 For penicillin sensitive children substitute aureomycin or chloramphenicol as streptococcicides giving daily doses of 25 mg per kilogram of body weight (1 capsule of 250 mg after each meal and at bed time for the child weighing 75 lbs) for the first seven days of each month

13 Concurrently with antibiotic and for an additional week prescribe antihistamine Depending on the age size and tolerance of the youngster suggest doses of 100 to 200 mg daily of pyribenzamine or benadryl If drowsiness is encountered use the combination of antihistamine and adrenergen (pyribenzamine or benadryl with ephedrine p 4212)

14 Useless and obsolete as prophylactic agents are rheumatic fever vaccines and serums arthritis vaccine streptococcal vaccine and streptococcus bacteriophages

Immediate Care (Phase I)

1 Even on slightest suspicion of a Phase I attack advocate complete bed rest and institute general measures used for care of infected patient (p 67)

2 While rheumatic fever is not a reportable disease isolate the patient particularly from other children in a susceptible family Remember that the hemolytic streptococcus provocative of rheumatic fever is as infectious as that which produces scarlet fever

3 For antistreptococcal effect prescribe penicillin Give a priming oral dose of 500 000 units of crystalline potassium penicillin G in milk ice cream soup fruit juice tea or broth If expense is not a factor use candy medication such as spersoids (Lilly) of which one rounded teaspoonful is the equivalent of 50 000 units

4 Four hours after the priming dose start daily maintenance doses of 250 000 units every three hours

5 In the penicillin sensitive substitute aureomycin or chloramphenicol Give a loading dose of 50 mg per kilogram of body weight (1 75 gm for the child weighing approximately 75 lbs) If antibiotic is rejected orally try a rectal dose using double quantities dissolved in saline warmed and instilled with a male catheter and funnel

6 If aureomycin is not tolerated substitute chloramphenicol or terramycin

7 Four to eight hours after the loading dose of aureomycin or chloramphenicol start daily maintenance doses U e an amount equal to the priming quantity divided into 4 equal portions given at 6 hour intervals

8 Concurrently with antibiotic and for a period of at least two weeks after the la_t do e prescribe prophylactic antihistamine Give 4 daily doses each of 25 to 50 mg of pyribenzamine benadryl or one of their substitutes (p 4212)

9 Avoid salicylates iodides gold and sulfonamides Of the e only sulfonamides are demonstrably streptococcicidal and this antibacterial effect is better and more safely produced by administration of peni cillin aureomycin or chloramphenicol Each of the proscribed drugs has inherent toxicity is hyperallergenic has little potential for anti rheumatic efficacy and is capable of producing tuberculin type hyper sensitivity manifestations simulating lesions of acute rheumatic fever (p 4169)

10 The adv_ability of climatotherapy in convalescence from rheu matic fever remains debatable The facts a sembled during World War II and later by the Metropolitan Life Insurance Company throw some doubt on the relationship between the disea_e and climatic con ditions The collected data suggest that rheumatic fever may occur in any part of the United States there is more rheumatic fever and rheumatic heart disease in the allegedly low incident areas than was previously supposed claims of observers in specific areas offering particular advantages over other locations have not yet been sub stantiated by satisfactory scientific data once rheumatic fever is active there exists no proof that any climate alters the severity or duration of the disease or the outcome in any given instance (J A M A 137 420 1948) Against climatotherapy are psychologic and economic factors el ewhere detailed (p 3761)

11 Despite wide publicity the efficacy of large do es of vitamin C (200 to 300 mg daily) in rheumatic fever appears questionable In a eries of twenty even patients treated with large doses of ascorbic acid no influence of therapy on the cour_e of the disea e was observed

12 In convalescence institute or repeat suggestions as to prophylaxis

Continuing Care (Pha e II)

1 Following an initial Phase I of the rheumatic fever complex and particularly a recurrent Phase I do not be misled by the seemingly favorable response to therapy

2 Continue maintenance doses of antibiotic for a period of at least one month following cessation of all clinical manife tations There after resume prophylactic antibiotic therapy the first week of each month as outlined previously

3 Concurrently with each course of antibiotic order antihistamines as previously outlined Continue for at least one week after cessation of antibiotic therapy

4 Search for foci of infection after each individual Phase I episode Consult otolaryngologist Favor surgical intervention where indicated

9 Despite these precautions try to avoid seeding an anxiety neurosis

10 Provide for desensitization if the youngster exhibits allergic manifestations to allergens other than hemolytic streptococcus Particularly protect against drug food and pollen syndromes (p 4477)

11 Throughout the school year rid the upper respiratory passages of hemolytic streptococci by prescription of 250 000 units of crystalline potassium penicillin G in tablet form after each meal and at bed time for the first seven days of each month Repeat during the month if there is exposure to respiratory infection By this step alone recurrences of rheumatic fever were completely eliminated in susceptible children as against an attack rate of 11 to 19 per cent in control groups

12 For penicillin sensitive children substitute aureomycin or chloramphenicol as streptococcicides giving daily doses of 25 mg per kilogram of body weight (1 capsule of 250 mg after each meal and at bed time for the child weighing 75 lbs) for the first seven days of each month

13 Concurrently with antibiotic and for an additional week prescribe antihistamine Depending on the age size and tolerance of the youngster suggest doses of 100 to 200 mg daily of pyribenzamine or benadryl If drowsiness is encountered use the combination of antihistamine and adrenergen (pyribenzamine or benadryl with ephedrine p 4212)

14 Useless and obsolete as prophylactic agents are rheumatic fever vaccines and serums arthritis vaccine streptococcal vaccine and streptococcus bacteriophages

Immediate Care (Phase I)

1 Even on slightest suspicion of a Phase I attack advocate complete bed rest and institute general measures used for care of infected patient (p 67)

2 While rheumatic fever is not a reportable disease isolate the patient particularly from other children in a susceptible family Remember that the hemolytic streptococcus provocative of rheumatic fever is as infectious as that which produces scarlet fever

3 For antistreptococcal effect prescribe penicillin Give a priming oral dose of 500 000 units of crystalline potassium penicillin G in milk ice cream soup fruit juice tea or broth If expense is not a factor use candy medication such as spersoids (Lilly) of which one rounded teaspoonful is the equivalent of 50 000 units

4 Four hours after the priming dose start daily maintenance doses of 250 000 units every three hours

5 In the penicillin sensitive substitute aureomycin or chloramphenicol Give a loading dose of 50 mg per kilogram of body weight (1 75 gm for the child weighing approximately 75 lbs) If antibiotic is rejected orally try a rectal dose using double quantities dissolved in saline warmed and instilled with a male catheter and funnel

6 If aureomycin is not tolerated substitute chloramphenicol or terramycin

7 Four to eight hours after the loading dose of aureomycin or chloramphenicol start daily maintenance doses Use an amount equal to the priming quantity divided into 4 equal portions given at 6 hour intervals

8 Concurrently with antibiotic and for a period of at least two weeks after the last dose prescribe prophylactic antihistamine Give 4 daily doses each of 25 to 50 mg of pyribenzamine benadryl or one of their substitutes (p 4212)

9 Avoid salicylates iodides gold and sulfonamides Of these only sulfonamides are demonstrably streptococcicidal and this antibacterial effect is better and more safely produced by administration of peni cillin aureomycin or chloramphenicol Each of the proscribed drugs has inherent toxicity is hyperallergenic has little potential for anti rheumatic efficacy and is capable of producing tuberculin type hyper sensitivity manifestations simulating lesions of acute rheumatic fever (p 4169)

10 The advisability of climatotherapy in convalescence from rheu matic fever remains debatable The facts assembled during World War II and later by the Metropolitan Life Insurance Company throw some doubt on the relationship between the disease and climatic con ditions The collected data suggest that rheumatic fever may occur in any part of the United States there is more rheumatic fever and rheumatic heart disease in the allegedly low incident areas than was previously supposed claims of observers in specific areas offering particular advantages over other locations have not yet been sub stantiated by satisfactory scientific data once rheumatic fever is active there exists no proof that any climate alters the severity or duration of the disea_e or the outcome in any given instance (J A M A 137 420 1948) Against climatotherapy are psychologic and economic factors elsewhere detailed (p 3761)

11 Despite wide publicity the efficacy of large
(200 to 300 mg daily) in rheumatic fever a[illegible]
series of twenty even patients treated v[illegible]
acid no influence of therapy on the cour[illegible]

12 In convalescence institute or rep[illegible]

Continuing Care (Pha_e II)

1 Following an initial Phase I [illegible]
particularly a recurrent Phase I [illegible]
favorable response to therapy [illegible]

2 Continue maintenance c[illegible]
one month following cessa[illegible]
after resume prophylact[illegible]
month as outlined prev[illegible]

3 Concurrently wit[illegible]
as previously outline[illegible]
of antibiotic therapy [illegible]

4 Search for foci [illegible]
Consult otolaryngolc[illegible]

5 Attempt to increase general resistance Correct anemia by dietary measures reinforced with hematinics if necessary (p 3897) Sugg[est] heliotherapy either natural or artificial (p 3794) Continue bed rest until temperature has been normal for a period of at least ten days until blood sedimentation rate is normal and leukocytosis has abated.

6 If the child has lost a significant period of school attendance favor a holiday for remainder of term Extreme efforts to catch up with the class may lead to tenseness fatigue and recurrence Institute or repeat suggestions for prophylaxis

Continuing Care (Phase III)

1 With onset of Phase III and classical manifestations of rheumatic fever continue or resume bed rest

2 Encourage parents by emphasizing the much less ominous prognosis in private practice as compared with institutional experiences (p 194)

3 Institute or re institute general measures for care of infected patients (p 67)

4 Obtain blood count urine blood culture blood sedimentation rate and if possible an electrocardiographic tracing for future comparison

5 Assure elimination of causative hemolytic streptococci by continuance or resumption of antibiotic therapy Prefer penicillin aureomycin or chloramphenicol as previously outlined

6 Continue or resume concurrent antihistamine as previously outlined

7 For symptomatic relief rely on hydrotherapy and physiotherapy Give sponges for antipyretic effect use local heat or counterirritation to painful joints and give opium substitutes for analgesia (12 to 25 mg of de[me]rol or 1 25 to 2 5 ... [me]thadolophine every three to four hours if needed)

8 Reserve salicylates ... use minimum dosage ... acetyl salicylic acid in capsules ... hours as needed Do not give iodides ... avoid sulfonamides ... toxicity is hype... and is cap... simula... efficacy ...

...ple[te] bed res[t] ... patient (p ...

2 ... toms If driven to salicylate ... span of time Favor

pat... every 3 4 6 8 or ... [sche]dule

... each of these ... [he]patotoxic potential

Unless prompt and dramatic improvement is noted with artisone and percorten—ascorbic acid abandon therapy after three or four con secutive daily injections

11 Undesirable side effects of hormones may be encountered in children with previously damaged hearts and manifestations of actual or threatened backward failure Retention of water and salt may cause urgent distress requiring discontinuance of hormone and use of mer curial diuretics (p 4305) excessive potassium loss may require intro duction of potassium chloride For oral use prescribe 0 6 gm every four hours if renal function is normal In an emergency inject sub cutaneously or by slow intravenous infusion 2 gm dissolved in 100 cc of 5 per cent dextrose in distilled water

12 If symptoms persist and cortisone and ACTH cannot be obtained consider use of para aminobenzoic acid PABA is without significant toxicity and it does not produce allergic hypersensitivity reactions so far as is presently known Given orally in enteric coated tablets of 0 5 gm up to a daily total of 24 gm for the adult and proportionately less for younger children PABA posse ses anti rheumatic properties somewhat analogous to salicylates

13 Treat cardiac complications as they develop (p 196) but remem ber that digitalis has no prophylactic value and may prove embar rassing to the normal or compensated circulation (p 854)

14 Consider carefully all aspects of the infection before terminating bed rest (p 196) Continue immobilization longer than in the manage ment of other infectious diseases unless the child is excessively rest less and unmanageable If possible maintain bed rest for at least ten afebrile days and until blood count is normal and erythrocyte sedi mentation rate approaches normality

15 In convalescence immediately prepare to complete the cycle by carrying out measures indicated under the heading of Prophylaxis

Continuing Care (Progressively Unfavorable Course)

1 With a continued unfavorable course despite therapy previously outlined suspect mechanical disturbances such as increasing back ward failure (p 941) and/or superimposition of subacute bacterial endocarditis with an antibiotic insensitive organism

2 Look for evidences of backward failure (hydrothorax peripheral edema engorgement of liver cardiac irregularity progressive myo cardial changes best demonstrated electrocardiographically) Consider therapy aimed at improvement of circulatory efficiency (p 945)

3 Obtain repeated blood cultures If a bacteremia is demonstrable test organism against available antibiotics Institute therapy as outlined under subacute bacterial endocarditis (p 1021)

4 In convalescence revert to Prophylactic Treatment

RHEUMATOID ARTHRITIS

(Atrophic, Proliferative or Infectious Arthritis)

Principles of Diagnosis and Therapy

1 Two observations one by a pathologist and the other by a therapist place rheumatoid arthritis in the definite category of tuberculin type allergic hypersensitivities (p 4169) Rich basing his conclusions on human autopsy material and on experimentally produced hypersensitivities revealed the similarity between rheumatoid arthritis and other syndromes of like pathogenesis particularly rheumatic fever and Hench by his demonstration that exudative and proliferative features of rheumatoid arthritis are reversible regularly produced remissions with injections of cortisone and ACTH

2 Although clinical manifestations of rheumatoid arthritis have been regarded as predominantly articular (Fig 753 p 2912 Fig 754 p 2914 and Fig 755 p 2915) most patients reveal widespread lesions common to other recognized hypersensitivity syndromes These include valvular defects myocardial changes secondary anemia pleural and pericardial effusions scleroderma and lymphadenopathy with hepatosplenomegaly (Still s Disease Felty s syndrome)

3 Whereas emphasis previously was focussed on differences between rheumatic fever and rheumatoid arthritis current interest is directed to their similarities In each syndrome the patient presents aseptic pyrexia abacterial arthropathy endocardial myocardial pericardial and peripheral vascular disturbances anemia leukocytosis increased erythrocyte sedimentation rate and periods of remission punctuated by episode of exacerbation

4 Differences between rheumatic fever and rheumatoid arthritis viewed in the above light appear more apparent than real more quantitative than qualitative Rheumatoid arthritis occurs more often in young adults rather than children Phase I is less clearly defined Phase II is less clearly apparent and is of longer duration in Phase III the joint involvement of rheumatoid arthritis is more likely to be polyarticular and more apt to involve smaller joints exudative phenomena are less likely to resolve and more apt to progress to cicatrization with joint deformity limitation of motion and eventual ankylosis periarticular changes are more advanced with greater muscle atrophy endocarditis and myocarditis are less prominent but peripheral vascular disturbances dominate the circulatory aspect of the disease systemic manifestations particularly fever are apt to be of a lower order of magnitude but of longer duration and the anemia is more marked and more persistent In the Phase IV in contradistinction to the complete resolution of the process in rheumatic fever the joint of the patient with rheumatic arthritis shows persistent chronic inflammatory disturbances eventually terminating in deformity and limited if not lost motion

5 All that has been said of the therapy of rheumatic fever applies equally to the management of the patient with rheumatoid arthritis

6 Pending availability of newer preparations possessing the poten tial of cortisone and ACTH main reliance still must be placed on non specific measures including psychotherapy rest home physio therapy dietotherapy occupational therapy breathing exercises extir pation of foci of infection and corrective orthopedic surgery (pp 2918–2924) Particularly should efforts be directed at correction or preven tion of deformity by scrupulous attention to posture in standing sitting and reclining (p 3492) corrective exerci es (p 3757) proper shoeing (p 3081) and provisions for rest in extension by use of removable splints bandages and casts

7 To the previous list of useless measures now may be added mas sive doses of vitamin D (ertron) and the Russian anti reticulocytotoxic serum (ACS)

8 As in rheumatic fever antibiotics (penicillin aureomycin and chloramphenicol) serve merely to eliminate sensitive bacteria partic ularly hemolytic streptococci when these behave as sensitizing aller gens Antihistamines merit use for prevention of acute histamine type hypersensitivity manifestations especially from prescribed antibiotic There is general agreement that salicylate has only palliative value and iodide therapy has more or less become obsolescent (p 4177)

9 We have found no reason to alter our previous opinion concern ing gold therapy which we approach with little enthusiasm and great fear (p 2922) This pe simistic viewpoint is sustained by two small but carefully studied series reported by Friedman and Steinbrocker and by Browning and his colleagues (New Eng J M 240 362 1949 and 237 428 1947) The former studied eighteen patients of whom one had a complete remission later followed by relapse two were slightly improved and fifteen showed no change though later two entered into inactive phases of the disease In the Browning experience with forty seven patients 25 per cent were improved 60 per cent showed no change and 15 per cent appeared to be worse Of his forty seven patients almost two thirds developed toxic manifestations Of these there were two instances of exfoliative dermatitis with one death (approximately 2% treatment mortality)

10 The results claimed by advocates of chrysotherapy are not suffi ciently impressive to offset the findings of the less enthusiastic Thus Cecil who advocates several series or courses with intervals of four to eight weeks claims remissions in only 31 per cent great improvement in 35 per cent moderate improvement in 20 per cent and no improve ment in 14 per cent However the e favorable results are somewhat less impre sive when the investigator admits to a 40 per cent relapse rate in those who did well and an over all toxicity of 25 per cent

11 The weakne ses of gold therapy are the more apparent when results are compared with those of cortisone and ACTH Whereas the latter produce improvement in a time as brief as a few hours gold courses must be given over a span of no less than three months and more often up to one to two years

12 We still maintain that chrysotherapy is best reserved for the patient who is progressing unfavorably and who is willing to take the

risk of drug toxicity Many individuals would rather be dead than incapacitated and they choose heroic forms of therapy Others more timid in their reactions prefer safety to risk particularly in view of the 75 per cent favorable course in the natural evolution of the disease (p 4346)

13 The details of chrysotherapy are elsewhere discussed (p 4346) We continue to be impressed by the toxicity of gold despite the fact that BAL provides effective antidotal therapy (p 4251) We believe with Archer that beneficial results of gold therapy are dependent on liver damage that patients improve in proportion to the degree to which hepatic function suffers as in remissions produced during the course of virus hepatitis and pregnancy

14 For those who feel that chrysotherapy is justifiable current preparations of choice include

Gold and Sodium Thiosulfate (Sanocrysin Abbott Merck Searle) marketed in ampuls containing 10 25 50 75 and 100 mg of 37 4% solution for intravenous injection

Gold Sodium Thiomalate (Myochrysine Merck) marketed in 1 cc ampuls containing 10 25 50 and 100 mg of the salt or approximately half as much gold for intramuscular injection

Aurothioglucose (Solganol B Schering) marketed in ampuls of 1 5 cc containing 10 25 and 50 mg of a 50% oily suspension for intra muscular injection

15 Of available products smaller doses are recommended than were previously given For example Cecil advocates a first intramus cular injection of 10 mg a second of 25 mg a third of 50 mg and a maximum of 100 mg given once a week until a total of 750 to 1000 mg has been introduced in a single course To prevent immediate reac tions most advocates of chrysotherapy favor intramuscular rather than intravenous introduction All warn of the necessity for following phys ical signs and laboratory examinations of urine and blood for early detection of toxicity There is general agreement that therapy should be interrupted at the first sign of toxicity and that BAL should be admin istered immediately that serious or progressive manifestations of poison ing become apparent (p 4251) There is also general agreement that weekly injections suffice and that there should be intervals of four to eight weeks between courses of which there apparently should be no fewer than two

Practical Management

1 Those who find themselves in agreement with stated viewpoints concerning the etiology and mechanisms productive of rheumatoid arthritis will institute therapy according to details laid down for manage ment of Phase III of rheumatic fever (p 4500)

2 Until cortisone and ACTH are more widely distributed steroid therapy may be attempted with the commercially available compound artisone (Wyeth) This substance known to chemists for twelve years is chemically 21 acetoxypregnenolone or delta 5 pregnene 3 21-diol 20 1 21 acetate Tested on a preliminary group of fifteen patients 80 per

cent responded favorably Advanced long standing rheumatoid arthritis appeared not to react well at all In the patients tested none of the objectionable side effects of cortisone and ACTH were observed (Seifter)

3 For those patients who are not progressing favorably despite the routine suggested gold therapy merits consideration according to *principles previously discussed* (p 4346)

4 In convalescence as in rheumatic fever institute or reinstitute suggestions detailed for prophylaxis

RHINOSCLEROMA

Principles of Diagnosis and Therapy

1 Whether or not rhinoscleroma is a specific infectious disease remains presently unknown (p 2109)

2 Certainly the condition is unsightly and a source of embarrassment to the patient (Fig 986B p 3359)

3 On the basis of a single case report from the Mayo Clinic treatment may be undertaken with streptomycin

RHINOSPORIDIOSIS

Principles of Diagnosis and Therapy

1 Rhinosporidiosis is one of the infrequently observed systemic mycoses (p 489) The characteristic visible lesion is a friable polyp resembling a cock s comb which may appear on the skin or a mucous surface such as nose ears eyes larynx vagina or penis

2 Rhinosporidiosis occurs particularly in those who e work brings them in contact with stagnant water The diagnosis is established by finding spore filled sacs in infected tissues

3 Direct initial efforts at excision or cauterization of individual lesions

4 If unsuccessful in eradication of polyps resort to systemic therapy with pentavalent antimonials (p 4224) Greatest experience has been with neostibosan (Winthrop) injected intravenously in 5% solution or intramuscularly in 25% solution As an initial do e the adult is given 0 2 gm If there is no untoward reaction the dose is increased to 0 3 gm and a course of eight to ten injections is completed by daily injections or every second day until a total of 2 to 4 gm has been administered

RICKETTSIALPOX

[Kew Gardens Spotted Fever]

Principles of Diagnosis and Therapy

1 Rickettsialpox is a newly described disease due to *Rickettsia akari* It is transmitted to man by the bite of a rodent mite *Allodermanyssus sanguinis* The common house mouse is the reservoir of infection

2 The disease is heralded by a primary lesion which usually is found on covered parts of the body though it may occur on neck face arms or dorsum of hands It first appears as a firm red papule at the site of the mite's bite Later the primary lesion develops into a deep seated vesicle which ultimately shrinks and dries to form a black eschar much like that seen in tsutsugamushi fever

3 About a week after appearance of the primary lesion the systemic phase of the disease is inaugurated by an abrupt onset of fever chills sweats and backache At this time examination reveals enlargement of regional lymph nodes and remnants of primary inoculum

4 The course of the disease is characterized by fever with morning remissions and afternoon rises to 103 or 104° F Febrile manifestations persist for about a week

5 Just after onset of fever or several days later a generalized maculopapular eruption is observed At first lesions are discrete and erythematous Later vesicles develop in summits of papules Eventually these dry to form black crusts which ultimately fall off without scarring The rash may be scanty moderate or abundant It has no distinct pattern of distribution and may appear first on arms legs abdomen back face or chest It has not been observed on palms or soles

6 The duration of the rash varies from two to ten days At its height there is usually some enlargement of the spleen

7 There are no unusual laboratory findings in rickettsialpox At most there is a moderate leukopenia which disappears two weeks after the patient has been afebrile

8 So far rickettsialpox has not been followed by complications or sequels The diagnosis is established in specially equipped laboratories by complement fixation tests

9 Despite its benign character rickettsialpox merits treatment with aureomycin and chloramphenicol Either of these preparations produces rapid defervescence and cure although the eruption may pursue the identical course observed in the untreated patient For the initial priming dose prescribe 25 to 50 mg per kg of body weight (1 75 to 3 5 Gm for the average adult weighing 150 lbs) For maintenance daily doses an identical amount is suggested Patients who fail to defervesce in twenty four or thirty six hours may be given larger quantities

ROCKY MOUNTAIN SPOTTED FEVER

[Spotted Fever Mountain Fever Bull Fever Black Fever Blue Fever Tobia Fever of Colombia Choix or Pinta Fever of Mexico]

Principles of Diagnosis and Therapy

1 Rocky Mountain spotted fever is a tick borne rickettsemia characterized by a generalized eruption (Fig 58 p 378)

2 The laboratory diagnosis is e tablished by the Weil Felix reaction and by virus neutralization and complement fixation tests (p 372 and 379)

3 Artificial active immunity is accomplished by injection of vaccine Specific antibiotic therapy is accomplished with chloramphenicol aureomycin and para aminobenzoic acid

Practical Management

Prophylaxis

1 Avoid tick bites by wearing tight fitted clothing Insect repellents and insecticides are of little value against ticks

2 As soon as discovered remove adherent ticks which usually do not begin to feed for several hours Avoid contamination of hands by using forceps or preferably a cigarette or a lighted match applied to the tick body After removal of tick cauterize area of bite with phenol or silver nitrate If neither is available scrub vigorously with soap and water

3 Rocky Mountain spotted fever vaccine prepared from membranes of embryonated chick eggs infected with Rickettsia rickettsii is now commercially available (Lederle Squibb) The suspension is formalin inactivated after which it is extracted with ether to remove yolk lipids and tissue debris The result is a solution that is almost water clear However despite precautions taken in preparation of vaccine a certain amount of egg protein remains Therefore question patient before injection concerning sensitivity to eggs

For active immunity of hypoallergic patients inject 1 cc subcutaneously or intramuscularly at weekly intervals for 3 doses Give a booster do e each spring and early summer at times when ticks are most active If more rapid immunity is required inject two doses each of 2 cc at an interval of five days

For patients who require active immunization and who are hyperallergic particularly to egg protein obtain vaccine made from t ssues of infected ticks by applying to United States Public Health Service Hamilton Montana

Immediate Care

1 Institute non specific measures for treatment of infected patients (p 68–73)

2 Order an initial priming do e of 50 mg of chloramphenicol or

aureomycin per kilogram of body weight (3 5 gm for average adult weighing 150 lbs) Administer 2 products every few minutes with milk soup or cream cheese until full amount has been ingested

Continuing Care (Favorable Course)

1 Maintain antibiotic level by giving 50 mg of chloramphenicol or aureomycin per kilogram of body weight per day in four or six equally divided doses Thus for the average adult weighing 150 lbs, effective maintenance is accomplished by oral administration of two products every three hours omitting 3 A M dose

2 Continue maintenance doses until patient has been afebrile for at least forty eight and preferably seventy two hours

Continuing Care (Unfavorable Course)

1 If course of disease is unaffected by the chosen antibiotic order double doses or add an equal amount of the one not chosen

2 If the chosen antibiotic produced gastric irritation, substitute the opposite number

3 In the rare instance of patient intolerance or organism resistance to both chloramphenicol and aureomycin resort to para aminobenzoic acid Administer the antibiotic orally in a priming dose of 100 mg per kilogram of body weight (7 gm or 14 tablets of 0 5 gm each for average adult weighing 150 lbs) Simultaneously suggest alkaline drinks to prevent excessive acidification of urine

4 If the priming dose of PABA is tolerated orally maintain levels with doses of 2 gm every two hours day and night Examine urine and blood carefully during PABA administration Should total white count fall below 3 000 discontinue PABA and deposit penicillin to prevent complications due to agranulocytosis (p 109b) Should urine contain heavy precipitation of PABA crystals order increasing amounts of fluid and bicarbonate

5 If PABA is rejected orally pass a duodenal tube and try trans duodenal introduction of antibiotic dissolved in bicarbonate of soda

6 If enteral administration fails set up an intravenous drip and introduce the priming dose of 7 gm by infusing 350 cc of 2% solution in physiologic saline

Continuing Care (Progressively Unfavorable Course)

1 In rare instances combined antibiotic therapy may be required Give equal parts of chloramphenicol and aureomycin as mentioned above or either or both supplemented by PABA

2 In desperation consider use of hyperimmune Anti Rocky Mountain spotted fever rabbit serum (Lederle) This heterologous product is supplied in ampul vials which yield 20 cc of serum when restored to original volume with contents of another ampul containing 20 cc of pyrogen free sterile distilled water Prior to injection test patient with 1 10 dilution of rabbit serum introduced intracutaneously and by ophthalmic instillation If non sensitive inject lyovac hyperimmune

heterologous rabbit erum intramu_cularly in a dose of 20 cc Sensi tive patients are best not treated with serum since potential benefits are feeble compared to risks

3 Obsolete remedies include Rocky Mountain spotted fever human convalescent serum penicillin metaphen and particularly sulfonamides which may accentuate manifestations presumably as the result of super imposed hyper-ensitivity

RUBELLA

[German Measles Epidemic Poseola]

Principles of Diagnosis and Therapy

1 German measles is a dermatropic viral infection that has neither complications nor mortality for the patient It is characterized by the combination of eruption (Fig 66 p 317) enlargement of post auricular occipital and cervical lymph nodes and mild systemic manifestations followed by complete recovery

2 Unfortunately rubella is a genetic carrier It may produce con genital deformities in the offspring particularly when the mother suf fers the attack during the first trimester of pregnancy (Gregg)

3 Among complications _een in infants born of mothers who had the disease during pregnancy are congenital cataract partial or com plete deafness abnormalities of the brain cardiac abnormalities con genital glaucoma abnormally small eyes severe squint inflammations of the deeper membranes of the eyes nystagmus cleft palate harelip cretinism mongolian idiocy enlargement of the ears enlargement of the breasts and defects of ribs teeth hands or feet

4 Babies born of mothers having rubella in the first trimester of pregnancy reveal congenital defects in 87 per cent of all instances There are 42 per cent of abnormalities if the disease occurred in the econd trimester of pregnancy and probably none during the third trimester

RELATION OF CONGENITAL DEFECTS TO TRIMESTER OF PREGNANCY

Infantile Congenital Defect	First Trimester	Second Trimester	Third Trimester
Cataract	17	0	0
Congenital heart disease	17	1	0
Deafne s	12	1	0
Malformed teeth	3	2	0
Mental defect	7	0	0
Spina bifida and hydrocephalus	3	0	0
Congenital defects of the gastro inte tinal tract	2	1	0
Blindne s	1	2	0
Miscellaneous	11	2	0

5 Because of the grave consequences to the fetus of maternal rubella the following prophylactic recommendations merit consideration

(a) Expose female children deliberately to German measles during their pre childbearing ages

(b) Recommend therapeutic abortion unless there are religious scruples to the contrary for all mothers who acquire German *measles during the first or second trimesters of pregnancy*

(c) If interruption of pregnancy cannot be accomplished for one reason or another attempt protection of the fetus by injecting the mother with human convalescent serum preferably obtained from one who has recently recovered from the disease employing *intramuscular injections of 50 to 100 cc* as often as material can be obtained

(d) If human convalescent serum is not obtainable substitute gamma globulin for at least three intramuscular injections in 10 cc dosage or placental globulin in double this quantity

6 *Mothers who have had the tragic experience of bearing* children with congenital defects as a result of rubella may be assured that subsequent offspring are in no danger of similar occurrence (Bass Bull N Y Academy of Medicine Dec 1948 798)

RUSSIAN FOREST SPRING DISEASE

(Russian Spring Summer Encephalitis Russian Tick Borne Encephalitis Russian Endemic Encephalitis Russian Far East Encephalitis)

General Principles of Diagnosis and Therapy

1 Russian forest spring disease is one of many non suppurative encephalomyelomeningitides (p 442) of specific viral origin

2 *The clinical manifestations are not characteristic* hence the diagnosis is established epidemiologically and serologically (p 445)

3 The virus is probably insect borne The most likely vector is a wood tick

4 Prophylaxis is best accomplished during an outbreak by avoidance of tick bites and their removal before they have fed (p 4507)

5 Activated virus vaccine has been prepared and is said to be effective

6 Successful *specific* therapy has been *claimed for* hyperimmune goat serum

7 Should the disease be seen in America it is suggested that it be treated as St Louis or American encephalitis (p 4310)

SALICYLATE

Whereas there is little to be added to what already is known of the pharmacology and therapeutics of the salicylates (pp 194 3833) the production of chronic tuberculin like allergic hypersensitivities by salicylate is a cause for considerable apprehension on the part of many practitioners (p 4169)

Despite enthusiasts who favor massive dose salicylate therapy by oral or intravenous routes in rheumatic fever (p 4498) we are among those who believe that the drug must be withheld pending further investigation (p 4178) The reasons leading to these conclusions are fully detailed in the paragraphs devoted to Anti therapeutic Devices earnestly recommended for careful study (p 4133)

SALMONELLOSIS

[Paratyphoid Fever]

Principles of Diagnosis and Therapy

1 The group of salmonelloses include various gram negative bacillary invasions cause by *S paratyphi* (paratyphoid A) *S schottmuelleri* (paratyphoid B) *S enteridis S cholerae suis* and *S suipester* (hog cholera paratyphoid c) and *S typhimurium* (*aertrycke*)

2 Salmonellosis occurs very frequently Most often it is characterized by diarrhea usually termed food poisoning (p 240) dysentery the trots or ptomaine poisoning Unless stools cultures are made the diagnosis is not established By the time the organism is grown subcultured and identified the patient has usually recovered

3 In the vast majority of instances the attack is relatively benign and self limited without complications or mortality (p 239)

4 On infrequent occasions salmonellosis simulates typhoid fever in duration severity and complications (p 4620)

5 As in typhoid fever epidemics of salmonelloses may exhibit respiratory manifestations including interstitial pneumonitis

Practical Management

1 Prophylactic use of vaccines such as the previously official typhoid paratyphoid vaccine is no longer advised Because of the many existent subspecies failure of cross immunization and severity of reactions to injection the Council on Pharmacy and Chemistry 1948 has omitted triple vaccine from its roster

2 Prevention is best accomplished by hygienic measures in food handling and preparation (p 243)

3 Mild attacks of salmonellosis require only symptomatic therapy

4 Dysentery like infections are managed as shigelloses (p 4520) since salmonellae also are sensitive to chloramphenicol (p 4279)

5 More severe invasions with generalized bacteremic manifestations are treated as typhoid fever (p 4620)

6 Experimentally antibiotic therapy has been conducted with garlicin and LL 1 neither of which is commercially available

SANDFLY FEVER

[Three Day Fever Pappataci Fever Phlebotomus Fever Mediterranean Dengue Summer Influenza Hundskrankheit Soldaten Fieber Acclimatization Fever Endemic Gastro enteritis Climatic Gastro enteritis Chitral Fever]

Principles of Diagnosis and Therapy

1 Sandfly fever is a benign insect borne viremia with a high morbidity and no mortality

2 Because of its short duration (three days as a rule) only symptomatic therapy is required (p 480)

3 For prophylaxis insect repellents (p 4373) are of greatest value particularly if used after sundown when the Phlebotomus papatasii the vector begins its nocturnal flight

4 Experimentally an irradiated chicken embryo vaccine virus has been tried without success Since multiple attacks of the disease may be experienced even in a single year hope for lasting artificially induced active immunity would appear remote

SARCOIDOSIS

[Besnier Boeck Schaumann s Disease]

Principles of Diagnosis and Therapy

1 Sarcoidosis is a systemic disease which resembles non caseating tuberculosis in its histopathologic characteristics Despite continued interest in sarcoidosis and careful analyses of clinical manifestations the nature of the condition continues to be obscure

2 Most investigators continue to believe that sarcoidosis represents a clinical manifestation of a perverse response of host tissues to the protein of the tubercle bacillus In this the patient exhibits anergy rather than the more commonly encountered hypersensitivity reactions (p 4167) In all observed cases there is absence of skin response to large doses of tuberculin Additionally later development of clinical tuberculosis has been noted

3 Clinical manifestations of sarcoidosis include characteristic dermatoses (Fig 954 p 3263) uveoparotid fever lymphadenopathy enlargement of paratracheal and peribronchial lymph nodes pulmonary infiltrations and pleural and pericardial effusions To this list

ophthalmologı ts add nodular lesıons of eyelıds lacrımal glands con junctıvae epısclera cornea and especıally the uveal tract

4 Laboratory fındıngs ınclude absence of tubercle bacıllı ın sputum gastrıc contents and bıopsıed skın lesıons negatıve response to at least double quantıtıes of tuberculın ıntroduced ıntracutaneously ele vatıon of serum globulın and posıtıve response to the *Kveım test* The last ıs an ıntracutaneous reactıon to 0 1 cc of antıgen prepared from lymph nodes cutaneous ınfıltrates or tonsıls of patıents sufferıng from the dısease The antıgen ıs ınjected ıntracutaneously usually on the flexor surface of the forearm A posıtıve reactıon consısts of an ınfıl trated area wıth papule or nodule formatıon and later superfıcıal necrosıs wıth ulceratıon The posıtıve response may occur wıthın two weeks but may be delayed for several months In the event of a doubt ful response hıstologıc examınatıon of the papule demonstrates ıts tuberculoıd structure resemblıng the appearance seen ın the spon taneously developıng sarcoıd lesıon

5 The prognosıs of sarcoıdosıs ıs reported unıversally good so far as survıval ıs concerned However ophthalmıc lesıons may lead to consıderable vısual ımpaırment

6 There ıs general agreement that roentgen therapy and antı bıotıcs ıncludıng streptomycın accomplısh lıttle of benefıt As to the use of vıtamın D_2 (calcıferol) and dıhydrotachysterol as ın lupus vul garıs (p 4390) there ıs a general agreement that calcıferol merıts trıal

SCABICIDES

Many preparatıons are avaılable for the cure of scabıes In the fol lowıng table the merıts of the varıous products are dıscussed

SCABICIDES

Preparatıon	Comment
Balsam of Peru	Ineffectual and obsolete
Benylate	Lotıon benylate N N R ıs an offıcıal 25% emulsıon of benzyl benzoate
Benzyl benzoate U S P	Use as lotıon benylate above Not effectıve as a pedıculo cıde Avoıd use on face Otherwıse a preparatıon of choıce
Beta naphthol benzoate	More toxıc than preferred preparatıons
Cresol	Toxıc Obsolete
Danısh Oıntment	Tıme honored sulfıde preparatıon Not comparable wıth newer preparatıons of choıce
DDT	In 10% talc or solutıon Not as effectıve as other prepara tıons of choıce
Enbın N.N.R	An oıl ın water emulsıon of chlorophenotane ethyl amıno benzoate and benzyl benzoate
	Avoıd contact wıth eyes and other mucous surfaces Rub about 60 cc over the entıre ınvolved area
	After twenty four to forty-eıght hours remove wıth soap and water
	Repeat after one week, ıf necessary Wear uncontamın ated clothıng and lınen after applıcatıon.

SCABICIDES *(Continued)*

Preparation	Comment
Hexachlorocyclohexane	See kwell
Kwell (C S C)	1% hexachlorocyclohexane in vanishing cream base Both scabicidal and pediculocidal Preparation of choice
Pyrethrum N N R	27% ointment effective against mites and eggs may produce dermatitis and exfoliation. Occasional sensitivity renders pyrethrum less acceptable than other preparations of choice
Ronone (Abbott)	2% rotenone in a mucilage of quince seed, Irish moss and chloroform Effective as scabicide but not pediculocidal.
Sulfur	Available as cream foam applicators and ointment Effective as a scabicide but prone to cause treatment dermatitis Prefer less toxic preparations of choice
Tar	Not effective and messy Prefer newer preparations of choice
Tyroscabe (Sharp & Dohme)	36% solution of benzyl benzoate with 0 053% tyrothricin. Effective both as scabicide and bactericide but not pediculocidal Recommended for combination of scabies and marked secondary pyogenic infections

SCABIES

[The Itch]

General Principles of Diagnosis and Therapy

1 The diagnosis of scabies is established clinically by finding of characteristic burrows (Fig 900 p 3183) and by identification of the causative mite Sarcoptes scabiei (Fig 899 p 3181)

2 Many preparations are available for cure of scabies Success depends more on patient cooperation and prevention of reinfection than on the specific (p 4513)

3 In a certain number of instances scabies is associated with pediculosis and a single product to liquidate both organisms is distinctly valuable In other instances there is secondary pyogenic invasion of scabetic burrow requiring additionally use of an antibiotic No one product is capable of simultaneously attacking acari pediculi and bacteria although kwell is both scabicidal and pediculocidal and tyroscabe is scabicidal and bactericidal The practitioner makes his choice of preparation depending on attendant circumstances

4 The treatment of scabies has been immensely simplified since introduction of 1 2 3 4 5 6-hexa chlorocyclohexane marketed as kwell ointment in a 1% vanishing cream base

5 Kwell is both a scabicide and a pediculocide For relief of either disturbance approximately 25 to 50 gm of kwell ointment are rubbed into affected parts after a hot bath Thereafter the patient refrains from bathing or washing for twenty four hours

At the end of this period a full bath is taken and fresh underclothes

night clothes and linen are donned Treatment is repeated in one week if necessary

6 Kwell causes no local irritation Relatively massive doses of kwell however may produce fatal convulsions in animals

7 As second choice suggest the following routine using benzyl benzoate

(a) Take a warm bath Soap body thoroughly for at least ten minutes particularly scrubbing infected regions
(b) While body is still warm spread benylate with swab or brush Particularly apply medicament to lesions and nails
(c) Allow lotion to dry Then reapply to lesions and particularly in and around nails For children use a total of 60 to 90 cc for adults 120 to 180 cc per treatment
(d) Send clothes and bedding for sterilization
(e) Twenty four hours after treatment take a warm soak and put on clean clothing
(f) Repeat treatment if necessary always avoiding application to eyes

8 In addition to treatment of patient other members of the household and contacts must be examined and treated if re infection is to be avoided (ping pong scabies)

9 Treat scabies infestations complicated by bacterial infection with tyroscabe a 36% solution of benzyl benzoate containing 0 053% of tyrothricin

10 Relatively inefficient are older preparations such as balsam of peru and tar and DDT

11 Excessively toxic and relatively ineffectual are cresol Danish ointment pyrethrum sulfur and beta naphthol benzoate

SCARLET FEVER

Principles of Diagnosis and Therapy

1 Scarlet fever is another of the many clinical syndromes produced by hemolytic streptococci (p 171)

2 It differs from other hemolytic streptococcal invasions only in the rather constant appearance of its characteristic exanthem (Fig 18 p 164) and enanthem (Fig 20 p 177)

3 Scarlet fever is no more and no less infectious than other hemolytic streptococcal invasions despite the panic that is usually created by the appearance of the eruption (p 174)

4 Because of the efficacy of antibiotics in the prevention and control of hemolytic streptococcal infections there appears no present necessity for continuing u e of the Dick test (p 183) Chemoprophylaxis with penicillin has relegated to obsolescence active immunization with scarlet fever streptococcus toxins both plain and tannic acid precipitated Similarly antibiotics have replaced antitoxic sera previously

used for passive immunization There seems no present need to consider injections of Scarlet Fever Human Immune Serum NF or of Scarlet Fever Streptococcal Antitoxin USP although large doses of human gamma globulin (40 to 60 cc intramuscularly) appear to prevent complications when given early in the disease

5 As in rheumatic fever host tissues suffer invasion by hemolytic streptococci and evince allergic hypersensitivity manifestations to microbic antigen

6 In view of the striking resemblance between the acute attack of scarlet fever and Phase I of the rheumatic fever complex and of the possibility that Phases II III and IV may follow as in the infection characterized more by arthropathy and circulatory complications it is recommended that the principles of therapy recommended for rheumatic fever be followed exactly in the treatment of scarlet fever (p 4493)

7 In convalescence follow up visits are mandatory in order that the clinician early recognize chronic hypersensitivity manifestations particularly in endocardium and kidneys

SCHISTOSOMIASIS

(Hemic Distomiasis Bilharziasis Blood Flukes Bladder Flukes River Flukes)

General Principles of Diagnosis and Therapy

1 One of the few bright reports of World War II is Veterans Administration Technical Bulletin 10–36 which attests to the minor incidence of schistosomiasis in returning soldiers Except for personnel involved in the military occupation of Leyte and internees at Davao on Mindanao no significant numbers of infestations have been noted The total of the infected may be less than 5000

2 The latent phase of Asiatic schistosomiasis produced residual complaints in many of the 300 soldiers examined at Mason General Hospital These included abdominal discomfort weakness headache myalgia and nervousness Despite these complaints the men were in excellent physical condition Approximately one third of readmitted patients had ova in their stools

Practical Management

Immediate Care

1 The Technical Bulletin of the U S Veterans Administration recommends treatment with tartar emetic reserving stibophen (fuadin) for second choice

2 Because of the toxicity of antimonial the undernoted technic must be followed closely

(a) Mak[illegible] freshly prepared 0 5% solution of antimony potassium [illegible] in 5% dextrose

(b) Discard any solution that is not clear or one which contains sediment

(c) Sterilize freshly prepared solution by boiling for five minutes Do not place in autoclave

(d) Draw solution into barrel and then discard needle replacing it with a fresh needle not contaminated with solution since introduction of even small amounts of tartar emetic into the subcutaneous or perivenous tissues may produce a serious slough

(e) Slowly introduce the drug intravenously two or three hours after meals Provide for a rest period of an hour after injection Discontinue administration of drug if toxic symptoms develop

(f) Introduction of 0 6 mg atropine sulfate half hour before injection of antimonial decreases the cough that often results from administration of the anti infective agent

3 For first probatory dose give an exceedingly slow injection of 8 cc

4 If all is well give succeeding injection on alternate days Increase amount of each injection by 4 cc until a dose of 28 cc has been accomplished If the latter amount appears to cause difficulty give two injections of 14 cc each at hourly intervals

5 A complete course consists of a total of 444 cc of 0 5% tartar emetic

6 If significant toxicity occurs give the pharmacologic antidote BAL (p 4251)

Continuing Care (Favorable Course)

1 Reexamine patient after three months and repeat treatment course if necessary

Continuing Care (Unfavorable Course)

1 Reserve stibophen (fuadin) for those who cannot tolerate antimony potassium tartrate It has lesser toxicity but also is considerably less effectual

2 Give stibophen by slow intramuscular injection For initial dose deposit 1 5 cc for second dose twenty four hours later introduce 3 5 cc for the third dose give maximum dose of 5 cc at the end of another twenty four hours

3 If preliminary injections are well tolerated inject 5 cc intramuscularly every other day until the patient receives a total of 75 cc

4 In severer and more resistant infections with Japonicum larger doses are required Increase the initial probatory dose to 2 cc the second to 4 cc the third to 6 cc and the fourth to 8 cc given at twenty four hour intervals If the 8 cc dose is tolerated repeat injections every second day until a total of 100 cc has been given

5 Stibophen treatments may be repeated if necessary after a lapse of four weeks Should symptoms of antimony poisoning develop (p 752) use BAL as the pharmacologic antidote (p 4251)

6 In treatment resistant schistosomiasis those with great experience have tried pentavalent arsenicals notably ethylstibamine (neosti

bosan Bayer 693) stibamine glucoside (neostam) and the aromatic diamidines stilbamidine and pentamidine (as yet available only for investigational use) From present information pentavalent antimonials are not as efficacious as trivalent Experience with aromatic diamidines is insufficient for expression of opinion

7 Under experimental investigation is a new antibilharzial drug known as miracil D (nilodin), a thioxanthone derivative

Miracil D is given in minimum effective doses of 5 mg per kilo every twelve hours for five days Toxic symptoms are slight but the efficacy of the drug appears to be erratic curing some patients and failing to cure others Further reports on miracil D will be awaited with great interest

SEDATIVES AND HYPNOTICS

Chloral Hydrate

Increasing experience with sedatives and hypnotics has fortified our personal opinion that chloral hydrate U S P is the preparation of choice (p 3836) Toxic effects on cardiovascular and respiratory systems greatly exaggerated have not occurred within the realm of our experience Nor do we find chloral prescriptions particularly irritant to the stomach provided they are given well diluted with warm fluid

On the positive side of the ledger sedative doses of 0 3 gm (5 grains) and hypnotic doses of 0 6 to 0 1 gm (10 to 15 grains) are almost uniformly effectual and virtually devoid of toxicoderm side reactions idiosyncrasy and toxicity When economic factors are a consideration (as in the case of large institutions and those practitioners who dispense as well as prescribe) the lesser cost of chloral as compared with the more widely advertised barbiturates is a significant consideration

Antihistamines

Most antihistamines are additionally sedative and hypnotic (p 4212) For waking hours the sedative action of antihistamines is a deterrent at bedtime however sedation and hypnosis are added advantages particularly when allergic manifestations such as itching prevent sleep

Barbiturates

In addition to the list of barbiturates in Table 215 (p 3836) the Council on Pharmacy and Chemistry has accepted evipal sodium (hexylbarbital) delvinal (vinbarbital sodium) and butisol (butabarbital sodium) Evipal is available in ampuls containing 0 5 and 1 gm in powder form to be dissolved in sterile distilled water for intravenous anesthesia of short duration delvinal is available in capsules containing 0 03 0 1 and 0 2 gm and also in sterile solution of which each cc

contains 65 mg for parenteral injection butisol is marketed in cap sules containing 0 1 gm and as an elixir in which each cc is the equivalent of 0 2 gm The actions of none of these preparations differs essentially from those previously described

SERUM ALLERGY

[Serum Sickness]

Serum sickne s is a less dramatic manifestation of allergic hyper sensitivity than anaphylactic shock (p 4187) The management of this allergic hypersensitivity follows along the lines established for pre vention of anaphylactic shock (p 4189) Additionally there is greater opportunity for the practitioner to provide palliation through admin istration of adrenergen and antihistamine

Principles of Diagnosis and Treatment

1 Prevent by adherence to the previous schedule (p 4190)

2 If prophylactic measures (pyribenzamine or benadryl for two weeks following the last injection of biological) have failed increase dose of prescribed preparation to tolerance (total 200 to 800 mg daily) Should hypersensitivity manifestations persist or should the patient develop side effects from antihistamine switch to a substitute such as neo antergen histadyl decapryn diatrin chlorotrimeton hydryllin neo hetramine tagethen thenylene thephorin or trimeton (Table p 4212)

3 In the presence of urgent symptoms (angioneurotic edema of tongue or larynx) inject benadryl intramuscularly or intravenously *using 2 to 5 cc (20 to 50 mg) Supplement antihistamine effect* with subcutaneous or intramuscular injection of adrenergen (epinephrine hydrochloride 1 1000 1% neosynephrin or 3% ephedrine)

4 In the presence of respiratory embarrassment prepare for emer gency tracheotomy (pp 3958 3993 and 3957) preferably after transfer of patient to hospital

5 If the combination of antihistamine and adrenergen fails set up an intravenous drip and deliver 1 gm of procaine hydrochloride (novocaine) in 500 cc of physiologic saline solution (add 100 cc of 1% procaine or 50 cc of 2% procaine to sufficient diluent to make a volume of 500 cc)

6 In the event that serum sickness develops without previous pro phylactic u e of antihistamine inaugurate active treatment with oral pyribenzamine or benadryl

(a) If symptoms are not severe start with 50 mg four times daily increasing the dose if manifestations of hypersensitivity fail to disappear and the patient does not exhibit untoward manifestations of antihista mine therapy (p 4214)

(b) If symptoms are moderately severe start with maximum daily doses of antihistamine i e 600 to 800 mg and decrease the dose as soon as hypersensitivity appears to be controlled (p 4216)

(c) If symptoms are of maximum severity such as threat to the re piratory tract apply for cortone or ACTH and in meantime repeat di rections 3 5 and 4 above

SHIGELLOSIS

(Bacillary Dysentery)

Principles of Diagnosis and Therapy

1 Bacillary dysentery is a common cause for the ubiquitous trots suffered at one time or another by each of us

2 The bacteriologic diagnosis is rarely established since it requires stool cultures and subcultures by an experienced bacteriologist (p 140)

3 The shigelloses include several subvarieties Each is antigenically complex hence serologic findings are difficult of interpretation (p 245) the prophylactic vaccine (Parke Davis) is valueless since it is incapable of producing cross immunity and antiserums whether monovalent or polyvalent have limited value

4 Fortunately shigellas are sensitive to chloramphenicol aureo mycin streptomycin and soluble and insoluble sulfonamides in order of their usefulness

Practical Management

Prophylaxis

1 In the presence of an epidemic of bacillary dysentery treat pos sible contacts as if they had acute symptoms using methods of *Immediate Care* as outlined later

2 Notify Health officers who will institute a search for carriers particularly among food handlers

Immediate Care

1 Most patients with shigellosis suffer only mild clinical manife ta tions They are treated while ambulatory Those with moderate or severe symptoms require nursing care at home or preferably in the hospital (p 67)

2 Whether symptoms are acute or chronic mild or severe the organism must be attacked vigorously to prevent later difficulties and protect the community Order a priming dose of 60 to 100 mg per kilogram of body weight of chloramphenicol (4 to 7 gm for average adult weighing 150 pounds) Give 2 products every few minutes with milk ice cream cream chee e soup or fruit juice

3 If economy demands substitute oral sulfonamide Give equal parts of sulfadiazine or sulfamerazine with bicarbonate of soda if a soluble product is desired and thalamyd for the insoluble preparation of choice

4 If patient is dehydrated give an infusion of 2 units of plasma (p 3778) followed by 1000 cc of 5% dextrose in saline

5 If there is gastric intolerance precluding oral use of antibiotic inject intramuscularly 1 gm of streptomycin or give intravenously 50 to 100 mg of aureomycin hydrochloride (p 4241) or 2 5 gm each of sodium sulfamerazine and sodium sulfadiazine diluted to at least 200 cc with saline or molar lactate

6 Administer prophylactic doses of antihistamine preferably 200 mg daily of pyribenzamine or benadryl

Continuing Care (Favorable Course)

1 As soon as stomach is tolerant order maintenance doses of chlor amphenicol spreading the amount of the priming do e in 4 equal portions over twenty four hours

2 Encourage a high caloric intake of soft cooked foods or liquids Low residue diets of boiled milk and rice cocoa mashed potato spa ghetti and purees are most acceptable

Continuing Care (Unfavorable Course)

1 If symptoms persist but stomach is tolerant double dose of chlor amphenicol or give an equal amount of aureomycin additionally

2 If chloramphenicol is not tolerated substitute aureomycin in the same quantity

3 If neither product is tolerated inject intramuscularly 0 5 gm streptomycin thrice daily or sodium salts of soluble sulfonamide as previously described

Continuing Care (Progressively Unfavorable Course)

1 Set up an intravenous drip Continue chloramphenicol or aureo mycin orally or streptomycin intramuscularly Supplement the tolerated antibiotic with intravenous sulfonamide Give a priming dose as pre viously described Maintain levels with introduction alternately of 2 5 gm of sodium sulfadiazine or sodium sulfamerazine every six or eight hours as indicated

2 Watch urine and blood for evidences of sulfonamide toxicity (p 94)

3 In desperation consider injection of Antidysentery Heterologous Serum (Polyvalent) N N R (Parke Davis) Marketed in 20 cc vials 80 to 100 cc may be introduced in the intravenous drip after skin test ing (p 555) desensitization if necessary (p 4191) and dilution to 500 cc with saline

4 Obsolete is dysentery bacteriophage

5 Available only for investigation is garlicin

6 Persist with antihistamine for at least two weeks after discon tinuance of antibiotic

(c) If symptoms are of maximum severity such as threat to the respiratory tract apply for cortone or ACTH and in meantime repeat directions 3 5 and 4 above

SHIGELLOSIS

(Bacillary Dysentery)

Principles of Diagnosis and Therapy

1 Bacillary dysentery is a common cause for the ubiquitous trots suffered at one time or another by each of us

2 The bacteriologic diagnosis is rarely established since it requires stool cultures and subcultures by an experienced bacteriologist (p 140)

3 The shigelloses include several subvarieties Each is antigenically complex hence serologic findings are difficult of interpretation (p 245) the prophylactic vaccine (Parke Davis) is valueless since it is incapable of producing cross immunity and antiserums whether monovalent or polyvalent have limited value

4 Fortunately shigellas are sensitive to chloramphenicol aureomycin streptomycin and soluble and insoluble sulfonamides *in order* of their usefulness

Practical Management

Prophylaxis

1 In the presence of an epidemic of bacillary dysentery treat possible contacts as if they had acute symptoms using methods of *Immediate Care* as outlined later

2 Notify Health officers who will institute a search for carriers particularly among food handlers

Immediate Care

1 Most patients with shigellosis suffer only mild clinical manifestations They are treated while ambulatory Those with moderate or severe symptoms require nursing care at home or preferably in the hospital (p 67)

2 Whether symptoms are acute or chronic mild or severe the organism must be attacked vigorously to prevent later difficulties and protect the community Order a priming dose of 60 to 100 mg per kilogram of body weight of chloramphenicol (4 to 7 gm for average adult weighing 150 pounds) Give 2 products every few minutes with milk ice cream cream cheese soup or fruit juice

3 If economy demands substitute oral sulfonamide Give equal parts of sulfadiazine or sulfamerazine with bicarbonate of soda if a soluble product is desired and thalamyd for the insoluble preparation of choice

8 Investigate possibility of parathyroid tumor (p 1233) Look for primary growth in breast prostate or digestive tract

9 With data at hand consider differential diagnosis of skeletal tumors as listed in Table 150 p 2836

10 Refer patient to orthopedic surgeon for bone biopsy

11 Discuss surgical procedure

SMALLPOX

[Variola Alastrim Cotton Pox Para Smallpox]

Principles of Diagnosis and Therapy

1 Smallpox is a completely preventable disease There is no excuse for epidemics occurring in any civilized community (p 424)

2 Prophylactic vaccination with the virus of cowpox provides effective cross immunization (Fig 69 pp 430–431 and p 428) Vaccination is recommended as a mandatory procedure in infancy and every three to five years thereafter (p 4631)

3 Though statistically uncommon the gravity of postvaccinal encephalopathy and myelopathy is so great that concurrent administration of antihistamine for prevention of the tuberculin type of hypersensitivity reaction is warranted in every instance

4 As yet there is no specific antibiotic for use in the treatment of smallpox Nevertheless prophylactic use of penicillin aureomycin or chloramphenicol is highly recommended If these anti infective agents do nothing else they prevent or mitigate secondary infections particularly of cutaneous pustules In addition chloramphenicol and aureomycin are virucidal and may possibly have some specific efficacy if given in priming and daily maintenance doses as large as 100 mg per kilogram of body weight (7 gm for the average adult weighing 150 lbs)

SNAKE BITE

Principles of Diagnosis and Therapy

1 There are in excess of 2000 species of snakes inhabiting the earth s surface and waters The terrestrial population of snakes must be enormous as any motorist who has traveled the roads of southern and western United States can attest

2 Of the snake population relatively few are venomous In North America the poisonous element is represented by corals copperheads water moccasins and rattlers In South and Latin Americas snake populations are very similar except that they bear different names as fer de lance barba amarilla cascabel bushmaster jararaca racucu urutu and corallilos (Coraes)

SILVER

Obsolete for internal use silver also is being replaced for local and topical application in the prophylaxis of ophthalmia neonatorum (p 4350) and the treatment of upper respiratory infections by antibiotics uch as penicillin bacitracin and tyrothricin

SIXTH DISEASE

[Exanthema Subitum Roseola Infantum Rose Rash Pseudorubella]

Principles of Diagnosis and Therapy

1 Roseola infantum in the opinion of experts is an almost universal infection for children under five years of age

2 A viremia sixth disease has an incubation period of ten to fifteen days with a single attack conferring permanent immunity

3 The febrile period lasts for three to nine days and terminates with appearence of the morbilliform eruption (p 412) Mild catarrhal otitis is the principal accompanying lesion

4 There is no available successful method of prevention or treat ment of exanthema subitum Fortunately the disease has neither sig nificant complications nor mortality

SKELETAL SYSTEM NEOPLASMS OF

Many neoplasms of bone are observed before subjective symptoms arise All are clearly demonstrable by simple roentgenography greatly facilitating diagnosis

Practical Management

1 During routine examination make note of any bony swelling or tenderness

2 In the presence of visible or palpable tumor of bone consider differential diagnosis of osseous swellings (p 2844)

3 Get blood for serodiagnosis of syphilis and malignancy (p 4431) acid phosphatase calcium total protein albumin-globulin ratio and erythrocyte sedimentation rate

4 *Inquire concerning pain* Consider differential diagnosis of ostealgia (p 281)

5 Get x rays of the chest particularly for evidences of tuberculosis

6 Get x rays of the bony tumor and compare with illustrative radiographs demonstrating bony malignancy (Figs 714–724 pp 2837–2848)

7 Look for evidences of pathologic fracture (p 2846)

8 Investigate possibility of parathyroid tumor (p 1233) Look for primary growth in breast prostate or digestive tract

9 With data at hand consider differential diagnosis of skeletal tumors as listed in Table 150 p 2836

10 Refer patient to orthopedic surgeon for bone biopsy

11 Discu s surgical procedure

SMALLPOX

[Variola Alastrim Cotton Pox Para Smallpox]

Principles of Diagnosis and Therapy

1 Smallpox is a completely preventable disease There is no excuse for epidemics occurring in any civilized community (p 424)

2 Prophylactic vaccination with the virus of cowpox provides effective cross immunization (Fig 69 pp 430–431 and p 428) Vaccination is recommended as a mandatory procedure in infancy and every three to five years thereafter (p 4631)

3 Though statistically uncommon the gravity of postvaccinal encephalopathy and myelopathy is so great that concurrent administration of antihistamine for prevention of the tuberculin type of hypersensitivity reaction is warranted in every instance

4 As yet there is no specific antibiotic for u e in the treatment of smallpox Nevertheless prophylactic use of penicillin aureomycin or chloramphenicol is highly recommended If these anti infective agents do nothing else they prevent or mitigate secondary infections particularly of cutaneous pustules In addition chloramphenicol and aureomycin are virucidal and may possibly have some specific efficacy if given in priming and daily maintenance doses as large as 100 mg per kilogram of body weight (7 gm for the average adult weighing 150 lbs)

SNAKE BITE

Principles of Diagnosis and Therapy

1 There are in excess of 2000 species of snakes inhabiting the earth s surface and waters The terrestrial population of snakes must be enormous as any motorist who has traveled the roads of southern and western United States can attest

2 Of the snake population relatively few are venomous In North America the poisonous element is represented by corals copperheads water moccasins and rattlers In South and Latin Americas snake populations are very similar except that they bear different names such as fer de lance barba amarilla cascabel bushmaster jararaca jararacucu urutu and corallilos (Coraes)

SILVER

Obsolete for internal use silver also is being replaced for local and topical application in the prophylaxis of ophthalmia neonatorum (p 4350) and the treatment of upper respiratory infections by antibiotics such as penicillin bacitracin and tyrothricin

SIXTH DISEASE

[Exanthema Subitum Roseola Infantum Rose Rash Pseudorubella]

Principles of Diagnosis and Therapy

1 Roseola infantum in the opinion of experts is an almost universal infection for children under five years of age

2 A viremia sixth disease has an incubation period of ten to fifteen days with a single attack conferring permanent immunity

3 The febrile period lasts for three to nine days and terminates with appearence of the morbilliform eruption (p 412) Mild catarrhal otitis is the principal accompanying lesion

4 There is no available successful method of prevention or treatment of exanthema subitum Fortunately the disease has neither significant complications nor mortality

SKELETAL SYSTEM NEOPLASMS OF

Many neoplasms of bone are observed before subjective symptoms arise All are clearly demonstrable by simple roentgenography greatly facilitating diagnosis

Practical Management

1 During routine examination make note of any bony swelling or tenderne s

2 In the presence of visible or palpable tumor of bone consider differential diagnosis of osseous swellings (p 2844)

3 Get blood for serodiagnosis of syphilis and malignancy (p *4431*) acid phosphatase calcium total protein albumin-globulin ratio and erythrocyte sedimentation rate

4 Inquire concerning pain Consider differential diagnosis of *ostealgia* (p *281*)

5 Get x rays of the chest particularly for evidences of tuberculosis

6 Get x rays of the bony tumor and compare with illustrative radiographs demonstrating bony malignancy (Figs 714–724 pp 2837–2848)

7 Look for evidences of *pathologic fracture* (p *2846*)

acteristic tail rattle and back markings in the shape of a baseball diamond copperhead are the characteristic copper color with alternating dark and light stripings water moccasins are an over all deep green with lighter green irregular bands Most if not all Solenoglypha (which include copperheads water moccasins and rattlers) have a characteristic hole or pit between nostrils and each eye

3 While efforts are being made to obtain and identify the offending snake the local site is examined for evidences of actual penetration since the character of the bite may suggest whether or not a venomous snake has been the re ponsible agent Non venomous snakes as a rule inflict a circular wound that is due wholly to bites from their teeth By contrast the venomous snake bite has lateral wounds outside of the circle that represent penetration of venomous fangs Finally the North American physician is assisted in his diagnosis by the local inflammatory reaction The North American rattler inflicts a wound that is painful swells rapidly and shows evidences of local hemorrhage due to presence of hemolysin and lysocythin By contrast the South American physician is faced with the problem of a painless and innocent looking wound which in no way gives testimony to the virulence of the neurocytolysin that has been injected

4 If the physician is certain that the bite has been inflicted by a nonvenomous snake treatment consists wholly in reassurance local application of antiseptic to the wound and use of a sterile dressing more for psychologic than surgical purpose

5 The treatment of snake bite due to a venomous species is considerably more complicated calling for both local and systemic therapy

6 Local treatment is facilitated if the emergency bag (p 3751) contains first aid equipment such as the commercially available Compakit (Cutter) Only slightly larger than the shell of a shot gun the Compakit contains a lymph constrictor a knife three suction cups antiseptic and full directions for use The lymph constrictor is applied 1½ inches above the wound to inhibit absorption of venom into the blood stream Fang marks and knife blade are painted with antiseptic after which cross cuts are made ¼ inch in length and ¼ inch in depth directly over each fang mark The mouth of suction cups and surrounding skin are moistened after which suction cups are applied to incisions and steady continuous suction is maintained

7 If it is necessary to improvise apply a tourniquet or ligature proximal to the bite With any available cutting edge incise fang bites to a depth of at least ¼ inch flush with any handy fluid and apply suction orally through a few layers of transposed gauze

8 If the patient is in severe pain or in a panic state sedate with 60 mg (1 grain) of phenobarbital or 50 to 100 mg of demerol given orally or by injection

9 If the patient is limp or comatose (as observed in rattlesnake bites of South America) avoid sedatives including alcohol

10 If not contained in emergency bag send for Crotalus antitoxin (North American snake bite serum) U S P This product marketed by Lederle and Wyeth is an antitoxic equine serum prepared by

3 Of the snakes of the Americas the North American coral and the Latin American corallilos (coraes) are classified as proteroglypha This species also includes sea snakes of Pacific and Indian Oceans cobras of India Burma and Malay tigers puff adders and copperheads of Australia and mambas and spitting cobras of Africa For these snakes no antivenin has as yet been perfected

4 Copperheads water moccasins and rattlers of the Americas are included in the Solenoglypha This species also embraces previously mentioned venomous snakes of Latin America green pit vipers of Asia habus of Japan davoias of India and viper puff adders and gaboom vipers of Africa For bites of Solenoglypha crotalus antivenin is available

5 Considering the total snake population of the Americas bites by venomous snakes are relatively uncommon It is estimated that no more than 2000 to 3000 occur annually in the United States of America with a mortality rate of 10 to 35 per cent The majority of American snake bite deaths probably occur in Florida and Texas where rattlers are particularly venomous Except in these areas the practitioner is more likely to be confronted with the problem of treating an anxiety or panic reaction than an actual snake bite poisoning

6 The venom of snakes is variously constituted Among preformed toxins are neurocytolysin hemolysin hemocoagulin proteolysin and cytolysin In addition lysocythin is formed at the point of contact as the result of reaction of venom with local tissues

7 Since proportions of toxin in venom vary with different species snake bite is not manifested by a single clinical entity Thus the South American rattler injects mostly neurocytolysin The victim notes little local reaction and few immediate systemic manifestations When evidences of poisoning appear after several hours they are particularly virulent with increasing somnolence usually followed by a terminal coma By contrast bite of the North American rattler produces marked local reaction with intense pain swelling and ecchymosis rapidly followed by systemic manifestations including vomiting somnolence and hemorrhages from any body cavity The insidious course of South American snake bite poisoning probably contributes to the high mortality whereas the intense local reaction to North American rattlers stimulates intensive first aid treatment and may account for the appreciably lower mortality rate

Practical Management

1 Because of the panic reaction that accompanies snake bite the practitioner s first duty is to determine whether or not there has been an actual bite and whether or not the offending snake belongs in the venomous group

2 Identification of the snake must rest on first hand evidence The practitioner should familiarize himself with venomous species of his neighborhood Corals are characterized by circular rings of blue yellow and red striped as in a barber pole rattlers have the char

SPIROCHETAL JAUNDICE

[Weil s Disease Leptospirosis Icterohemorrhagica Infectious Jaundice]

Principles of Diagnosis and Therapy

1 The syndrome previously labeled infectious jaundice or Weil s disease (p 360) is better termed spirochetal jaundice to distinguish it from homologous serum jaundice and from virus hepatitis (p 4635) formerly called catarrhal jaundice (p 1951)

2 Of the three types of specific hepatitis homologous serum jaundice is clearly recognized by the history of antecedent blood or plasma infusion spirochetal jaundice rarely observed in the United States is confined mostly to bargemen sewer workers wharf men fish workers miners slaughterhouse workers and others exposed to rats and responds almost specifically to penicillin virus hepatitis commonly encountered in private practice is resistant to antibiotics but may be aborted or modified if treated with gamma globulin in the long pre icteric period

Practical Management

1 Using what are now regarded as inconsequential doses of penicillin (15 000 to 50 000 units) specific therapeutic results have been observed in experimental and clinical spirochetal jaundice

2 With this background the physician currently confronted with the problem of treating spirochetal jaundice may confidently deposit 600 000 units of procaine penicillin G in aqueous suspension each day for at least a week

3 As a supplement to penicillin transfusions of whole blood from donors who have had Weil s disease are regarded by Patterson as the sheet anchor in the treatment of the severely ill patient

4 Sulfonamides and arsenicals are not effective Heterologous equine antileptospiral serum (p 4261) is obsolete Aureomycin and chloramphenicol merit trial on the basis of laboratory evidence of organism sensitivity

SPIROCHETICIDES

The efficacy and safety of penicillin as a spirocheticide constitutes one of the great contributions of the Golden Era of Therapeutics For ease of administration and safety there is nothing comparable Whether older products such as arsenic and bismuth will be retained to supplement penicillin therapy remains for the future to decide Certainly they add risk Whether they will give a sufficient increase in the percentage of cures to offset hazards can only be determined statistically after the lapse of a few years (p 4554)

immunization against the venom of snakes of the crotalus family which includes rattlers water moccasins and copperheads but not coral snakes

The combination package of antivenin contains one vial of antitoxic serum one vial of 15 cc of pyrogen free sterile distilled water for use as a diluent one sterile needle one vial of normal horse serum diluted 1 10 for ophthalmic and intracutaneous testing and for making dilu tions when desensitization is required and one applicator of iodine solution

11 As soon as antivenin has been obtained perform ophthalmic and intracutaneous tests for sensitivity with a 1 10 dilution (p 555)

12 While these data are being determined question patient as to sensitivity (p 4187) Inject at least 5 cc of 1% benadryl intramus cularly to prevent hypersensitivity reactions when antivenin is injected

13 If the patient has no significant hypersensitivity introduce 15 to 20 cc of antivenin in the vicinity of the bite and deposit 30 to 50 cc intramuscularly in buttocks or anterior abdominal wall Be prepared to repeat these injections every thirty to sixty minutes until symptoms subside

14 If the patient is hypersensitive weigh the relative risks of allergic phenomena and of snake bite poisoning

If necessary as a life saving measure antivenin may have to be given to the hypersensitive Under these circumstances inject benadryl every twenty to thirty minutes and keep epinephrine hydrochloride (1 1000) available in a second syringe for subcutaneous or intramus cular introduction if necessary Cautiously introduce intracutaneously 0 1 cc of 1 10 dilution of antivenin When the response has been determined choose other sites for injection and increase amounts to 0 2 cc if possible

15 As soon as undiluted antivenin is tolerated intracutaneously switch to subcutaneous or intramuscular injections meanwhile con tinuing benadryl and adrenergen as needed

16 In the treatment of bites by North American rattlers discontinue injections shortly after systemic symptoms appear controlled In the instance of South American rattlers however the insidious nature of the poisoning makes it imperative to continue therapy in the absence of overt clinical manifestations

17 If facilities are available and symptoms warrant set up an intra venous drip with 5% dextrose in saline To this add diluted antivenin if there is no apparent sensitivity In the event of anaphylactic pheno-mena inject epinephrine hydrochloride (1 1000) directly into the rub ber tubing below the drip for immediate intravenous introduction

With these modalities the organism destroys erythrocytes leukocytes and fixed cells and produces violent gastro intestinal distress Its *coagulase* prevents anti infective agents from diffusing into the lesion while spreading factor permits bacterial body and its toxin to extend by continuity and contiguity

5 In addition to these offensive qualities the staphylococcus is possessed of a remarkably adaptive mechanism It rapidly develops defenses against antibiotic agents particularly sulfonamides and peni cillin By these means it assumes the property of bacterial fastness and defies destruction by intended therapeutic agents (p 4133)

6 Staphylococcic invasiveness is not always determined by bacterial virulence and adaptability Even feebly offensive organisms such as the albus strain may gain access to host tissues when defenses are enfeebled Locally this may be the result of any break in the integrity of skin or mucous surface inadequacy of the circulation or macera tion particularly resulting from a primary fungus infection etc Sys temically general resistance may be enfeebled as the result of prematurity senility chronic or wasting di ease malnutrition anemia and *hyperglycemia or other metabolic disturbances*

7 Staphylococci may cause clinical manifestations through inges tion of preformed toxin (p 240) production of local pyoderms (p 3248) and initiation of mucosal lesions in the upper respiratory tract includ ing nasopharyngitis accessory nasal sinusitis tonsillitis pneumonitis lobar pneumonia otitis media mastoiditis otogenic and rhinogenic meningitis and conjunctivitis With markedly increased virulence or extremely lowered host resistance staphylococci may give rise to bacteremias with secondary metastatic furuncles and areas of suppura tion in lungs kidneys perinephric tissues bones and joints Finally a particularly resistant type of subacute bacterial endocarditis is pro duced when organisms of low virulence colonize on damaged heart valves (p 1021)

8 *Staphylococci exhibit marked sensitivity to sulfonamides peni cillin* bacitracin tyrothricin aureomycin chloramphenicol and strep tomycin Successful management however requires more than casual introduction of the potentially effective antibiotic agent To prevent survival of resistant or fast bacterial strains the attack must be launched with an overwhelming loading dose high antibiotic levels must be maintained for a prolonged period in order succe sfully to deal with hardy strains of surviving organisms host resistance must be reinforced by elimination of unfavorable factors and by strengthening defensive and offensive qualities Finally alternate or supplementary antibiotics must be available to eliminate fast strains which have successfully evaded destruction by the original therapeutic agent

9 The recovered patient does not develop a natural active immunity to the invading staphylococcus Neither can an artificially produced active immunity be accomplished with the many available commercial preparations *none of which have Council approval Included in this* list of ineffective and mostly obsolete products are staphylococcus bac teriophage staphylococcus immunogen staphylococcus streptococcus

SPIROCHETICIDES

Preparation	Comment
Arsenic	Trivalent organic preparations powerful but toxic despite antidotal efficacy of BAL (p 4251) If used, prefer oxophenarsine (mapharsen) and dichlorophenarsine (clorarsen) Pentavalent products (Tryparsamide) toxic and ineffectual
Aureomycin	Somewhat effective but not comparable to penicillin
Bismuth	Feebly effective but may supplement arsenic and perhaps penicillin.
Chloramphenicol	Somewhat effective but not comparable to penicillin.
Gold	Obsolete
Iodide	Of use only for resolution of gumma (p 334)
Penicillin	Most effective and safest. Use massive dosages Reserve therapy with arsenic and bismuth for treatment failures (p 4558)
Tryparsamide	See Arsenic

SPOROTRICHOSIS

Principles of Diagnosis and Therapy

1 Sporotrichosis is a systemic fungus infection (p 495) similar to actinomycosis

2 In most instances the diagnosis is established by isolation of the filamentous spore bearing fungus (p 487) from the initial lesion or chancre usually observed on fingers or dorsum of the hand (Fig 967 p 3312)

3 Sporotrichosis is said to respond readily to iodides administered orally Potassium iodide is recommended in slowly increasing doses up to 4 to 6 gm daily Recurrence can be avoided by extending treatment for one or two months after apparent cure

4 Iodide resistant infections may respond to sulfonamide

5 Fluctuant abscesses may be punctured but not incised

6 Roentgen therapy may be considered as in actinomycosis (p 4141)

STAPHYLOCOCCAL INFECTIONS

Principles of Diagnosis and Therapy

1 The ubiquitous staphylococcus may be grown from any skin or mucous surface (p 151)

2 Mere bacterial demonstration of staphylococci does not necessarily imply pathogenicity Most often the organism is a contaminant or a secondary invader

3 Primary staphylococcal pathogenicity is dependent on assumption of increased virulence by the invader and/or diminished host resistance

4 The virulent staphylococcus may secrete hemolysin leukocidin, necrotizing principle enterotoxin coagulase and spreading factor

With these modalities the organism destroys erythrocytes leukocytes and fixed cells and produces violent gastro-intestinal distress Its coagulase prevents anti infective agents from diffusing into the lesion while spreading factor permits bacterial body and its toxin to extend by continuity and contiguity

5 In addition to these offensive qualities the staphylococcus is possessed of a remarkably adaptive mechanism It rapidly develops defenses against antibiotic agents particularly sulfonamides and penicillin By these means it assumes the property of bacterial fastness and defies destruction by intended therapeutic agents (p 4133)

6 Staphylococcic invasiveness is not always determined by bacterial virulence and adaptability Even feebly offensive organisms such as the albus train may gain access to host tissues when defenses are enfeebled Locally this may be the result of any break in the integrity of skin or mucous surface inadequacy of the circulation or maceration particularly resulting from a primary fungus infection etc Systemically general resistance may be enfeebled as the result of prematurity senility chronic or wasting disease malnutrition anemia and hyperglycemia or other metabolic disturbances

7 Staphylococci may cause clinical manifestations through ingestion of preformed toxin (p 240) production of local pyoderms (p 3248) and initiation of mucosal lesions in the upper respiratory tract including nasopharyngitis accessory nasal sinusitis tonsillitis pneumonitis lobar pneumonia otitis media mastoiditis otogenic and rhinogenic meningitis and conjunctivitis With markedly increased virulence or extremely lowered host resistance staphylococci may give rise to bacteremias with secondary metastatic furuncles and areas of suppuration in lungs kidneys perinephric tissues bones and joints Finally a particularly resistant type of subacute bacterial endocarditis is produced when organisms of low virulence colonize on damaged heart valves (p 1021)

8 Staphylococci exhibit marked sensitivity to sulfonamides penicillin bacitracin tyrothricin aureomycin chloramphenicol and streptomycin. Successful management however requires more than casual introduction of the potentially effective antibiotic agent To prevent survival of resistant or fast bacterial strains the attack must be launched with an overwhelming loading dose high antibiotic levels must be maintained for a prolonged period in order successfully to deal with hardy strains of surviving organisms host resistance must be reinforced by elimination of unfavorable factors and by strengthening defensive and offensive qualities Finally alternate or supplementary antibiotics must be available to eliminate fast strains which have successfully evaded destruction by the original therapeutic agent.

9 The recovered patient does not develop a natural active immunity to the invading staphylococcus Neither can an artificially produced active immunity be accomplished with the many available commercial preparations none of which have Council approval Included in this list of ineffective and mostly obsolete products are staphylococcus bacteriophage staphylococcus immunogen staphylococcus-streptococcus

vaccine combined staphylococcus toxoid and staphylococcus vaccines both autogenous and stock

10 Passive immunization using staphylococcus antitoxin is also a feeble and now obsolete therapeutic effort

11 In striking contrast to discouraging results with vaccines and serums is the wide choice of potent antibiotic agents For local and topical therapy we favor bacitracin and tyrothricin in solution or ointment form Both products have great potency negligible tendency for the production of hypersensitivity and negligible toxicity unless introduced parenterally (p 4247) For systemic use we favor penicillin for *first choice with aureomycin or chloramphenicol for supplementary* or alternate prescription We oppose local use of sulfonamide for reasons elsewhere given in detail (p 4544) We reserve systemic sulfonamide therapy for staphylococcal infections if failure is encountered with penicillin aureomycin and chloramphenicol Sulfonamide has inherent toxicity there is a marked tendency for bacteria to become fast and *finally both acute histamine type and chronic* tuberculin type allergic hypersensitivity manifestations occur more commonly with sulfonamides than with any other antibiotic (p 4179)

Practical Management

Prophylaxis

1 For reasons previously stated place no reliance on injection of staphylococcal antigen for the production of artificial active immunity In the rare instance where a known heavy contamination with staphylococci has occurred (as surgically when a finger is pricked during incision and drainage of a pyoderm) resort to chemoprophylaxis Introduce intramuscularly 300 000 to 600 000 units of crystalline procaine penicillin G in aqueous suspension and repeat at 12 to 24 hour intervals for a period of three to five days

Immediate Care

1 *Of clinical disturbances caused by staphylococci food poisoning* alone requires no specific therapy The violence of the ensuing vomiting and diarrhea can be counted on to remove preformed toxin and since bacterial body has not been introduced there is no rationale for use of antibiotic agents

2 Except in the management of the relatively mild *and isolated* pyoderm (furuncle) do not place main reliance on local or topical therapy There is no objection to wet dressings or ointments of bacitracin (p 4247) or tyrothricin (p 4622) but we oppose direct introduction of these or other antibiotics into the inflammatory area If antibiotic is introduced parenterally it is best given in an *indifferent area* using a dose sufficiently large to provide for adequate antibiotic levels in infected as well as other tissues

3 With the exceptions above noted favor parenteral injection of a massive loading dose of penicillin Depending on the severity and

extent of the lesion and the state of host resistance introduce an intramuscular priming dose of 300 000 to 1 200 000 units of crystalline procaine penicillin G in aqueous or oily suspension the latter with or without 2% aluminum monostearate Maintain blood and tissue penicillin levels with subsequent injections of amounts equal to the priming do e at 8 12 or 24 hour intervals as indicated by the clinical respon^e

4 In the penicillin sensitive substitute aureomycin or chloramphenicol Give a heavy loading dose approximating 100 mg per kilogram of body weight (7 gm for the average adult weighing 150 lbs) Give 2 products every few minutes with fruit juice ice cream milk carbonated water tea or broth until the entire quantity has been ingested If the stomach is intolerant of aureomycin substitute chloramphenicol If neither is tolerated improvise a solution by dissolving double the oral dose in warm saline Introduce rectally by means of a funnel attached to an inserted male catheter Hold buttocks firmly together for at least fifteen minutes to prevent expulsion particularly in children

5 If aureomycin and chloramphenicol are not tolerated rectally or orally consider intravenous injection of 100 to 500 mg of the special aureomycin hydrochloride prepared for intravenous u e Dissolve in 0 75% sodium carbonate solution as provided by the manufacturer

6 For third choice in the initial treatment of staphylococcal infection give soluble sulfonamide A atisfactory loading oral do^e is 2 to 3 gm each of sulfadiazine and sulfamerazine with a teaspoonful of bicarbonate of soda For intravenous introduction dissolve 2 5 gm each of sodium sulfadiazine and odium sulfamerazine in 200 to 500 cc of sterile physiologic aline or molar lactate

7 Concurrently with penicillin or sulfonamide give prophylactic antihistamine therapy u ing daily doses of 200 to 400 mg of pyribenzamine or benadryl Continue for at least two weeks after the last dose of antibiotic

8 In localized pyoderms or other staphylococcal infections look for neighboring sites of lessened resistance Seek areas of dermatophytosis and treat concurrently with fungicides (p 4331) evaluate the efficacy of the local circulation and seek to improve by surgical or mechanical means perform a careful and complete physical examination and do urine and blood tests Correct anemia hyperglycemia glycosuria malnutrition and other detectable disturbances

9 In respiratory infections summon the consultant rhinolaryngologist *Particularly* request a survey of the nasal accessory sinuses for detection of undrained inflammatory areas Institute local instillations or irrigations with bacitracin or tyrothricin solution

Continuing Care (Favorable Course)

1 Do not be deceived by rapid responses to therapy Maintain antibiotic levels and adjuvant measures of therapy for a period of at least ten to fourteen days after subsidence of symptoms

2 When evidences of acute inflammation have abated correct or

eliminate factors productive of local or systemic diminution in host resistance Warn the patient of possible recurrence unless general hygienic conditions are maintained at a high level

Continuing Care (Unfavorable Course)

1 In the presence of continuing or recurrent infection bacteremia metastatic pulmonary furunculosis perinephric abscess pyo arthritis osteomyelitis subacute bacterial endocarditis and otogenic or rhinogenic meningitis resort to a combined attack on the invading organism

2 Increase the dose of penicillin If intramuscular deposits are to be continued give 600 000 units of crystalline procaine penicillin G in oil with 2% aluminum monostearate every 6 8 12 or 24 hours If an intravenous drip can be established introduce 1 to 25 million units of crystalline potassium penicillin G in saline intermittently or continually through each 24 hour period Supplement penicillin with aureomycin or chloramphenicol By the oral method approximate 100 mg per kilogram of body weight (7 gm for the average adult weighing 150 lbs) divided into four equal parts given at approximately 6 hour intervals If the intravenous drip is established inject into the rubber tubing 100 to 500 mg of aureomycin hydrochloride during the course of the continuous penicillin infusion

3 If the patient is penicillin sensitive or intolerant of aureomycin and chloramphenicol use sulfonamide for supplementation If the intravenous drip is established alternate penicillin or aureomycin hydrochloride with soluble sulfonamide using 2 5 gm each of sodium sulfamerazine and sodium sulfadiazine in 200 cc of diluent at 8 12 or 24 hour intervals depending on patient response Carefully examine urine and blood for evidences of sulfonamide poisoning (p 94)

4 Look for feeding foci in skin and respiratory passages When high antibiotic blood and tissue levels have been established surgically drain or excise infected areas Particularly look for evidences of suppurative spheno ethmoiditis mastoiditis purulent arthritis suppurative osteomyelitis perinephric abscess pulmonary or pleural suppuration and suppurative endophlebitis particularly of the sinuses adjacent to mastoid and nasal accessory structures (p 1447)

5 Fortify patient resistance by intravenous introduction of plasma protein hydrolysate or blood as indicated

6 If possible isolate the particular invading staphylococcus from local lesions blood or cerebrospinal fluid Request laboratory tests for sensitivity to various available antibiotics Concentrate on introduction of what appears to be the most effective therapeutic agent

STB

STB a trivalent derivative of acetarsone (4 oxy 3 acetylaminophenyl arsenoxide) is used in Africa for peroral mass therapy of frambesia (yaws) It is not currently available in the United States

The dose of STB is 10 to 20 mg per kilogram of body weight administered orally each day for five consecutive days In the experiences of Friedheim (Am J Trop Med 29 185 1949) STB produced cicatrization in all instances of infectious yaws and in fourteen of fifteen persons afflicted with crab yaws (p 4330)

STEROGYL

Sterogyl is used in the treatment of leprosy in Brazil Capsules containing 15 mg are given three times the first week then twice a week for two or three weeks Thereafter the dose is reduced to once a week

Sterogyl is not currently available in the United States where the treatment of leprosy is conducted with sulfones (p 4387)

STREPTOCOCCAL INFECTIONS

Principles of Diagnosis and Therapy

1 The family of streptococci is numerous and diverse The majority of streptococci are saprophytes which may be grown at any time from most skin and mucous surfaces as well as from feces (p 158)

2 Streptococci vary in virulence non hemolytic alpha (viridans) and gamma (fecalis) organisms are infrequently pathogenic whereas the hemolytic beta variety is most often invasive In the presence of active inflammation resulting from one of the less pathogenic organisms assume that there is local or systemic diminution of host resistance

3 Paradoxically less virulent alpha and gamma varieties of streptococcus are relatively more resistant to antibiotics (especially penicillin) than more virulent hemolytic sub-species When invasion with alpha and gamma varieties occurs therapy must be more intensive and prolonged as for example in subacute bacterial endocarditis (p 4313)

4 Streptococci vary in their production of toxins Among soluble poisons which they secrete are streptolysin which hemolyzes blood cells leukocidin which destroys white cells fibrinolysin which dissolves fibrin hyaluronidase which liquefies one of the components of connective tissue and an erythrotoxin which produces the characteristic rash of scarlet fever (Fig 18 p 164 Fig 20 p 177)

5 Antiserums which neutralize one variety of toxin do not necessarily neutralize others It is for this reason that streptococcal antitoxic serums and toxin immunizations proved inadequate even in the days that preceded antibiotic therapy and Dick testing for erythrogenic toxin is obsolete (Fig 181)

6 By contrast anti infective agents attack the organism which produces toxin In this regard they are indirectly effective as anti

toxic agents since they destroy the toxin factory though they have no demonstrable effect on free toxin previously liberated

7 Like staphylococci streptococci possess a 'spreading factor' This determines in part the ability of microbes to invade tissues beyond the point of inoculum Spreading factor may be particularly operative in lymphangitis (p 3962)

8 In addition to their offensive qualities streptococci are possessed of remarkably adaptive defensive mechanisms much like staphylococci They rapidly develop resistance to anti infective agents especially sulfonamide and to a lesser degree penicillin (p 4133) Fortunately sulfonamide fast organisms are usually not penicillin resistant and microbes sensitive to both antibiotics yield to aureomycin and chloramphenicol

9 The determinant in streptococcal infection is not always bacterial virulence Just as often diminution of host resistance permits even feebly invasive organisms to produce inflammatory phenomena Host factors which invite or permit streptococcal invasion include diminished local resistance due to breaks in the continuity of skin or *mucous membrane maceration resulting from prior infection by* viruses fungi or other bacteria and inadequacies of the local circulation Diminished systemic resistance also may result in streptococcal invasion particularly when the host is malnourished premature senile anemic hyperglycemic glycosuric or the victim of some wasting disease

10 Once streptococci have gained access to the tissues they may cause a variety of clinical manifestations They may produce a local inflammatory process such as abscess wound infection nasopharyngitis tonsillitis otitis media puerperal or postabortal endometritis and breast abscess The reaction may spread by continuity or contiguity giving rise to lymphangitis lymphadenitis accessory nasal sinusitis mastoiditis otogenic or rhinogenic meningitis peritonitis pleuritis or pneumonitis *Organisms may grow in the blood stream in a streptococcemia* or they may colonize on a damaged heart valve as in subacute bacterial endocarditis (p 4313) or in the lumen of a vein as in cavernous or lateral sinus thrombosis (pp 1447 and 2130)

11 In addition to their inherent invasiveness streptococci also function as allergens As such they may produce histamine type and tuberculin type hypersensitivity reactions In this manner hemolytic streptococci are important factors in the pathogenesis of rheumatic *fever* rheumatoid arthritis lupus erythematosus erythema nodosum nephropathies and many other syndromes hitherto believed of unknown etiology (p 4169)

12 Finally when invasion *toxemia bacteremia and hypersensitivity* reactions combine clinical syndromes of the greatest complexity develop as particularly exemplified in rheumatic fever (p 4171)

13 Fortunately streptococci are sensitive to sulfonamides and many antibiotics including penicillin bacitracin tyrothricin aureomycin chloramphenicol and streptomycin Successful management however requires more than casual introduction of the potent thera

peutic product To prevent survival of resistant or fast bacterial strains the attack must be launched with an overwhelming loading dose High antibiotic levels must be maintained for a prolonged period of time in order successfully to deal with hardy strains of surviving organisms Host resistance must be reinforced by elimination of unfavor able factors and by strengthening defensive and offensive qualities Alternate or supplementary antibiotics must be available to eliminate fast strains which succe sfully evade destruction by the original therapeutic agent and additionally the clinician must deal at all times with the hazard of sensitization of host ti sue to microbic antigen For this rea on antibiotics must be accompanied by antihistamines for possible prevention of allergic lesions Later when proliferative and exudative hypersensitivity manifestations become apparent (as in rheumatoid arthritis and rheumatic fever) the therapeutic armamen tarium requires reinforcement with cortisone or ACTH

14 The recovered patient does not develop a natural active immunity to the family of streptococci Neither can artificial active immunity be produced by available commercial preparations none of which have Council approval Included in the list of ineffective and mostly obso lete products are streptococcus bacterophages and vaccines and scarlet fever toxins

15 Passive immunization using streptococcal antitoxin is also a feeble and now obsolete therapeutic endeavor Included in the list of abandoned preparations are erysipelas streptococcus antitoxin scar let fever streptococcus antitoxin anti erysipelas antibacterial serum human scarlet fever immune serum and rheumatic fever antiserum

16 In striking contrast to discouraging results with vaccines and serums is the efficacy of antibiotic agents For local and topical therapy we favor bacitracin and tyrothricin in solution or ointment form Both products have great potency negligible tendency for production of hypersensitivity and negligible inherent toxicity unless introduced parenterally

17 For systemic use we favor penicillin for first choice with aureo mycin or chloramphenicol for supplementary or alternate prescription We oppose local use of sulfonamide for reasons elsewhere given in detail (p 4544) We oppose systemic sulfonamide therapy because of inherent toxicity of the antibiotic its marked tendency to induce bac terial fastness and most significantly because of the tendency of the antibiotic to produce histamine type and tuberculin type allergic hypersensitivity manifestations that may be identical with those caused by the microbe which the anti infective agent seeks to eliminate

18 For treatment of special streptococcal infections see scarlet fever septic sore throat and rheumatic fever

Practical Management

Prophylaxis

1 For reasons previously stated place no reliance on injection of streptococcal antigen for production of artificial active immunity In

the rare instance where a known heavy contamination has occurred (as surgically when a finger is pricked during incision and drainage of an inflammatory lesion) resort to chemoprophylaxis Introduce intramuscularly 300 000 to 600 000 units of crystalline procaine penicillin G in aqueous suspension Repeat at 12 to 24 hour intervals for a period of three to five days

Immediate Care

1 *Except in the management of relatively mild and isolated local* lesions do not place main reliance on local or topical therapy There is no objection to wet dressings or ointments of bacitracin or tyrothricin but we oppose introduction of antibiotics directly into the inflammatory area If antibiotic is introduced parenterally it is best given in an indifferent site using a dose sufficiently large to provide for adequate antibiotic levels in infected as well as other tissues

2 With the exception above noted *favor parenteral injection* of a massive loading dose of penicillin Depending on the severity and extent of the lesion and the state of *host resistance* introduce an intramuscular priming dose of 300 000 to 1 200 000 units of crystalline *procaine penicillin G in aqueous or oil suspension* the latter with or without 2% aluminum monostearate Maintain blood and tissue levels with subsequent injections of amounts equal to the priming dose at 8 12 or 24 hour intervals as indicated by the clinical response

3 To the penicillin sensitive give aureomycin or chloramphenicol Prescribe a heavy loading dose approximating 100 mg per kilogram of body weight (7 gm for average adult weighing 150 lbs) Give 2 products every few minutes with fruit juice ice cream milk carbonated water tea or broth until the entire quantity has been ingested

4 If the stomach is *intolerant of aureomycin* substitute chloramphenicol or terramycin

5 *If neither antibiotic is tolerated orally improvise a solution* by dissolving double the oral dose in warm saline Introduce rectally by *means of a funnel attached to an inserted male catheter* Hold buttocks firmly together for at least fifteen minutes to prevent expulsion particularly with children

6 If aureomycin and chloramphenicol are not tolerated orally or rectally consider intravenous injection of 100 to 500 mg of aureomycin hydrochloride for intravenous use Dissolve in 0 75% sodium carbonate solution as provided by manufacturer

7 Concurrently with antibiotic given prophylactic antihistamine therapy Use daily doses of 200 to 400 mg of pyribenzamine or benadryl Continue for at least two weeks after last dose of antibiotic

8 With localized lesions look for neighboring sites of lessened resistance Seek areas of dermatophytosis and treat concurrently with fungicides (p 4331) Evaluate efficacy of local circulation and seek to improve by surgical or mechanical means Perform a careful and complete physical examination and do urine and blood tests Correct anemia hyperglycemia glycosuria malnutrition and other detectable disturbances

9 In respiratory infections summon consultant rhino-laryngologist Particularly request a survey of nasal accessory sinuses for detection of undrained inflammatory areas Institute local instillations or irrigations with bacitracin or tyrothricin solutions

Continuing Care (Favorable Course)

1 Do not be deceived by rapid responses to therapy Maintain antibiotic levels and adjuvant measures of therapy for a minimum period of ten to fourteen days after subsidence of symptoms

2 When evidences of acute inflammation have abated correct or eliminate factors productive of local or systemic diminution of host resistance Warn patient of possible recurrence unless general hygienic conditions are maintained at a high level

Continuing Care (Unfavorable Course)

1 In the presence of continuing or recurring infection bacteremia metastatic pulmonary lesions perinephric abscess pyo arthritis osteomyelitis subacute bacterial endocarditis and otogenic or rhinogenic meningitis resort to a combined attack on the invading organism

2 Increase the dose of penicillin If intramuscular deposits are continued give 600 000 units of crystalline procaine penicillin G in oil with 2% aluminum monostearate every 6 8 12 or 24 hours If an intravenous drip can be established introduce 1 to 25 million units of crystalline potassium penicillin G in saline intermittently or continually throughout each 24 hour period Supplement penicillin with aureomycin or chloramphenicol By the oral method approximate 100 mg per kilogram of body weight (7 gm for the average adult weighing 150 lbs) Divide into 4 equal parts given at approximately 6 hour intervals If the intravenous drip is established inject into the rubber tubing 100 to 500 mg of aureomycin hydrochloride during the course of the continuous penicillin infusion

3 If the patient is penicillin sensitive or intolerant of aureomycin and chloramphenicol consider use of sulfonamide for supplementation If an intravenous drip has been established alternate penicillin or aureomycin hydrochloride with soluble sulfonamide using 2 5 gm each of sodium sulfamerazine and sodium sulfadiazine in 200 cc of diluent at 8 12 or 24 hour intervals depending on patient response Carefully examine urine and blood for evidences of sulfonamide poisoning (p 94) Look for manifestations of allergic hypersensitivity

4 When a high antibiotic blood and tissue level has been established surgically drain or excise infected areas Particularly look for evidences of suppurative sphenoethmoiditis mastoiditis purulent arthritis suppurative osteomyelitis perinephric abscess pulmonary or pleural suppuration and suppurative endophlebitis of sinuses adjacent to mastoid and nasal accessory structures (p 1447)

5 Fortify patient resistance by intravenous introduction of plasma protein hydrolysate or blood as indicated

6 If possible isolate invading streptococcus from local lesions

blood or cerebrospinal fluid *Request laboratory tests for sensitivity to various available antibiotics* *Introduce most effective therapeutic agent.*

7 *With superimposed allergic hypersensitivity manifestations* (including endocarditis myocarditis glomerulonephritis lupus erythematosus erythema nodosum periarteritis nodosa poly-arthralgias serous effusions in joints pleura pericardium or peritoneal cavities) follow suggestions for Phase III of rheumatic fever complex (p 4500)

8 *In convalescence* revert to suggestions for prophylaxis of rheumatic fever (p 4497)

STREPTOCOCCAL SORE THROAT

(Septic Sore Throat)

Principles of Diagnosis and Therapy

1 *Septic* sore throat is a hemolytic streptococcal invasion (p 185) usually epidemic and milk borne through bacterial contamination secondary to bovine mastitis

2 While manifestations of septic sore throat are usually due to organism invasion they may also include hypersensitivity phenomena simulating those observed in rheumatic and scarlet fevers (pp 135 and 171 Fig 20 p 177 and Fig 18 p 164)

Practical Management

Prophylaxis

1 Notify Health officers to survey milk routes Discontinue milk deliveries

2 Substitute powdered or canned milk for fresh product

3 Isolate patients as assiduously as those with scarlet fever (p 67)

Immediate Care

1 Institute nonspecific treatment of the infected patient (pp 68-73)

2 Inject intramuscularly a loading dose of 600 000 units of procaine penicillin G in aqueous suspension (p 4452)

3 Order 200 mg daily of pyribenzamine or benadryl orally If patient cannot swallow introduce 5 cc of 1% benadryl intramuscularly

4 Avoid sulfonamides which are less effective than penicillin (p 186) and impose the hazard of drug hypersensitivity (p 4179)

Continuing Care (Favorable Course)

1 Maintain penicillin levels with daily injections of 300 000 to 600 000 units procaine penicillin G for at least three days after defervescence

2 Continue antihistamine for two weeks beyond discontinuance of antibiotic

3 Check urine and heart weekly for at least six weeks

Continuing Care (Unfavorable Course)

1 With persistent symptoms double penicillin unitage

2 If the patient is sensitive to penicillin or the organism appears resistant substitute aureomycin or chloramphenicol rather than sulfonamide Give a priming dose of 100 mg per kilogram (7 gm or 28 products for the average adult weighing 150 pounds) Give 2 products every few minutes with milk cheese or ice cream until the entire amount is swallowed Sustain antibiotic levels with daily maintenance doses equal to the priming dose given in four equal portions at six hour intervals

3 Only in desperation resort to sulfonamides Give 1 to 2 gm each of sulfadiazine and sulfamerazine with bicarbonate of soda for the loading dose If the stomach is intolerant inject intravenously 2 5 gm each of sodium sulfadiazine and sodium sulfamerazine in 200 cc of diluent preferably molar lactate

STREPTOMYCIN

Available Products

Streptomycin (base) N N R Ampuls and vial containing 1 gm (Abbott, Cutter Heyden Lilly Merck Merrell Parke Davis Pfizer Raymer Schenley Sharpe & Dohme Squibb Upjohn Warner Wyeth) containing 5 gm (Merck Squibb) containing 10 gm (Upjohn)

Ointment (1 gm = 5000 micrograms) Bristol Requires refrigeration

Dihydrostreptomycin Vials 1 and 5 gm (Abbott Merck Parke Davis Squibb Upjohn Winthrop)

Neomycin—not commercially available

Dosage Therapeutics and Toxicity

See under tuberculosis pp 4608 to 4619

STRONGYLOIDIASIS

[Threadworm Infestation Cochin China Diarrhea]

Principles of Diagnosis and Therapy

1 Strongyloidiasis usually complicates uncinariasis (p 4624)

2 The diagnosis is established through identification of rhabditiform larvas in the stool (Fig 438 p 1904 lower right hand corner)

Practical Management

1 Treat uncinariasis first (p 4624) This may also eliminate strongyloides

2 If strongyloidiasis persists after eradication of hookworm use gentian violet as the anthelmintic of choice (p 4197)

3 Order the patient to swallow one hour before meals two 1½ hour Seal in tablets of gentian violet (each containing 32 mg) thrice daily for two days On the third and fourth days increase each dose to 3 tablets on the fifth and sixth days to 4 tablets and from the seventh to the twelfth days to 5 tablets or a daily total of 15 tablets (480 mg)

4 If intensive gentian violet therapy produces nausea vomiting or diarrhea omit the next dose and go back to the smaller amount, con tinuing maximum tolerated dose until the twelfth or preferably the eighteenth day if possible

5 In severe infections and in patients with gastric intolerance to gentian violet pass a duodenal tube daily for one week Each time give a transduodenal feeding of 2 5 cc of 1% aqueous gentian violet

SULAMYD [SULFACETIMIDE SODIUM]

An unofficial soluble sulfonamide (p 4546) widely used by oph thalmologists gynecologists and urologists

Available Products

Sulamyd Tablets 0 5 gm (Schering)
Sulamyd Solution (30%) (Schering)

Therapeutics

In urinary infections rapid excretions produce high levels Daily doses of 3 to 4 gm are usually employed

For ophthalmic use the 30% solution effects a concentration of 800 mg per cent in the cornea after instillation of one or two drops Sulamyd installation is suggested after removal of foreign bodies after trauma as a pre operative and postoperative prophylactic measure and in treatment of conjunctivitis caused by Staphylococcus aureus Koch Weeks bacillus pneumococci E coli E typhosa and gonococci

Quite likely Sulamyd will yield to aureomycin which covers a broader bacterial spectrum and is free from toxicity

Toxicity

As other sulfonamides (p 94)

SULFONAMIDES

Practitioners of the 1930 vintage will find it difficult to believe that sulfonamides miracle drugs of dawn years in the Golden Age of Therapeutics already are becoming obsolete and that their utter and complete abandonment would detract only slightly from over all efficacy of anti infective therapy Penicillin is capable of taking com

plete care of sulfonamide ensitive coccal invasions with the possible exception of meningococcemia and aureomycin and chloramphenicol are vastly superior to sulfonamide in gram negative bacillary invasions and viremias

Aside from the extraordinary therapeutic potentials of its relatively nontoxic rivals principal causes for diminishing use of sulfonamide are its inherent toxicity (p 94 Fig 15 p 90) its tendency to produce allergic hypersensitivities and the facility with which bacteria develop resistant or fa_t strains These limiting Anti therapeutic Devices (p 4133) require consideration before review of positive contributions to sulfonamide therapy

TOXICITY

The inherent toxicity of the sulfonamides includes untoward reac tions due to unforeseen idiosyncrasy and those resulting from frank overdosage In either instance sulfonamide poisoning may produce neurological disturbances drug fever toxicoderms blood dyscrasias toxic hepatitis crystalluria and urolithiasis (pp 94–96)

Efforts to Reduce Toxicity Several praiseworthy attempts have been made to reduce the toxicity of sulfonamides These include

1 Elimination of demonstrably toxic products such as sulfanilamide sulfapyridine sulfathiazole etc

2 Alkalinization of urine by administration of 2 gm of bicarbonate of soda with each gram of sulfonamide

3 Simultaneous administration of sulfonamide with sodium lactate The latter by increasing urinary *p*H favors solubility of free and con jugated forms of antibiotic

4 Implementation of Lehr s demonstration that several sulfona mides such as sulfathiazole sulfadiazine sulfamerazine and sulfapyra zine can be dissolved simultaneously in the same medium to the full extent of their separate saturation levels without the occurrence of precipitation Consequently combinations of partial dosages of two or more sulfonamides if compared with equal total amounts of single drugs showed substantially less tendency to intratubular deposition of crystals and thus to the development of renal obstruction This fact explains the strikingly low acute and chronic toxicity of sulfonamide combinations At identical total concentrations the *in vitro* antibac terial efficacy of the sulfonamide combinations is equal and sometimes superior to the activity of the single compounds

The use of combinations of partial dosages is best illustrated by Council approved trisulfazine (Central) containing 0 166 gm each of sulfadiazine sulfamerazine and sulfamethazine with sodium lactate This single product accomplishes full therapeutic potency with neg ligible danger of crystalluria and urolithiasis The incidence of crystal luria with the combined product is reduced to 6 per cent as against 29 per cent with sulfadiazine alone 28 per cent with sulfamerazine alone and 70 per cent with sulfathiazole alone Renal complications are reduced to zero with the combination as against 2 5 per cent with sulfadiazine 4 per cent with sulfamerazine and 5 5 per cent with sulfathiazole Toxicoderms and drug fevers occur in 2 per cent with

the mixture as against 3 per cent with sulfadiazine 5 per cent with sulfamerazine and 11 per cent with sulfathiazole

Comparison with Toxicity of Other Antibiotics Despite significant reduction in sulfonamide toxicity untoward manifestations remain disproportionately high when compared to the almost complete innocuousness of penicillin aureomycin and chloramphenicol

ALLERGIC HYPERSENSITIVITY

A second black mark against sulfonamide therapy is the relatively high incidence of hypersensitivity reactions These include immediate acute histamine type syndromes and less frequently encountered appalling and insidious chronic tuberculin type manifestations (p 4169) Under latter circumstances as detailed completely in the section on Allergic Hypersensitivity the therapist may contribute to or actually initiate a crippling if not lethal reaction simulating peri arteritis nodosa rheumatoid arthritis rheumatic fever abacterial endocarditis or diffuse lupus erythematosus

Additional observations which add to the menace of sulfonamide hypersensitivity reactions include the following observations

1 Hypersensitivity manifestations result from local or topical applications of small total quantities as well as oral or parenteral administration of full therapeutic doses

2 There is an increasing incidence of hypersensitivity with repeated exposures to drug antigen Thus occurrence of sulfonamide sensitivity is less than 8 per cent on first exposure but second administration increases the rate to 11 per cent

3 The period of incubation between administration of sulfonamide allergen and appearance of tuberculin type hypersensitivity may be weeks months or years The conscientious practitioner who lives his life with his patients may never feel completely at ease with those for whom he has prescribed sulfonamides Should one or more of the long roster of tuberculin type manifestations later develop (p 4169) from whatever cause he may not satisfactorily exonerate himself in his own eyes

4 Coexistence of symptoms of microbic invasion and those of bacterial and drug hypersensitivity create confusing problems for the therapist This is best illustrated in rheumatic fever (p 4171) in Phase I sulfonamide administration is demonstrably useful in preventing and combating streptococcal invasion in later phases during which rheumatic manifestations appear to result from sensitization to bacterial antigen administration of sulfonamide may intensify symptomatology presumably from allergic responses of host tissues to drug proteinate antigen

Comparison with Other Antibiotics The threat of sulfonamide hypersensitivity reactions looms most formidably when comparison is made with other antibiotics particularly penicillin aureomycin and chloramphenicol Each of the latter three to be sure is capable of producing acute histamine type hypersensitivity reactions most of which have mere nuisance value (urticaria and other toxicoderms drug

fever and eosinophilia) but there have not yet been reported experimental or clinical evidences that any of these potent anti infective agents is capable of inducing more serious chronic tubercular type syndromes

DEVELOPMENT OF BACTERIAL RESISTANCE OR "FASTNESS"

A third serious deterrent to sulfonamide therapy is the tendency of certain bacteria to develop an active immunity to the antibiotic agent Early in clinical experiences with sulfonamide therapy of gonorrhea it was noted that certain organisms became resistant to the therapeutic agent. Stated in another way certain strains of gonococci developed resistance or drug fastness to the extent that treatment became quite ineffectual (p 4133)

Comparison with Other Antibiotics The development of drug fast strains of bacteria is not unique with gonococci and sulfonamide The principle is illustrated also by tubercle bacilli when exposed to streptomycin (p 4610) However microbic immunity occurs rarely with penicillin aureomycin and chloramphenicol Further gonococci that exhibit bacterial resistance to sulfonamide are as sensitive to penicillin as other strains of Neisseria

SUMMARY

The counts against sulfonamides (particularly as compared to other antibiotics such as penicillin aureomycin and chloramphenicol) include the threats of idiosyncrasy toxicity hypersensitivity and development of bacterial resistance The status of sulfonamide therapy has been best summarized by Talbot (New York State J Med. 1948 p 283) in the following words

Sulfonamide should not be prescribed unless there is adequate clinical evidence to warrant therapeutic use Optimal amounts only should be given and excesses avoided The drug should be discontinued as soon as possible Finally sulfonamide should not be given if other methods of therapy are available which are equally efficacious It is apparent that the incidence of severe and untoward reactions from sulfonamides cause them to be considered potentially more harmful than penicillin With standardization of the doses of penicillin there has been no evidence forthcoming which shows that an excess of penicillin does any particular harm Sulfonamides on the other hand become increasingly toxic as the quantity increases

Preparations for Local and Topical Use

In the early years following its introduction into clinical medicine when sulfonamides were relatively unopposed as effectual anti infective agents the market was deluged with products intended for local and topical application Traumatic and surgical wounds both civil and military were quite regularly dusted with sterilized sulfonamide powder or crystals pharmaceutical manufacturers hastened to put forth a wide variety of products to include crystals micro-crystals dermal and

ophthalmic ointments nose drops shaving soaps after shave lotions hair tonics suppositories solutions troches lozenges dental cones packings and the like

In the text devoted to the pharmacology and therapeutics of the sulfonamides the Integrated Practice of Medicine (p 99) clearly expressed disapproval of indiscriminate use of sulfonamide preparations for local bacteriostasis or bactericidal activity The topical use of the sulfonamides has been enthusiastically exploited without due consideration of limitations and dangers The hopes and expectations of local bacteriostasis are not justified by theoretical or practical consideration The sulfonamides are not directly lethal to bacteria as is iodine They require tissue participation for their bacteriostatic and bacteriolytic proclivities and their therapeutic activity is lessened and almost nullified by the presence of pus blood dead bacteria and procaine an ester of para aminobenzoic acid

In addition to distinctly limited local parasitropism topical applications of sulfonamide possess demonstrable and theoretical hazards for the host They may cause the same toxicity as systemic doses they delay healing and they may produce sensitivity so that systemic employment at a future time may be precluded

The Council on Pharmacy and Chemistry 1947 added its official condemnation of sulfonamide products for local application Acceptance of preparations previously authorized was rescinded in keeping with the statement that Experience gained in World War II seems to indicate that the use of crystalline sulfonamides as topical agents was not very successful in the management of wound infection or in the treatment of infections of the skin or mucous membrane The routine use of sulfonamides as topical applications in wounds burns and in superficial infections is therefore to be discouraged The Council believes it necessary to emphasize again the potential hazards of the indiscriminate topical use of sulfonamide preparations Inquiries are being received concerning the local use of sulfonamides in conditions for which there is no evidence of their value such as hair tonics to control dandruff and promote growth of new hair in shave cream to prevent infection and in other equally inconsequential preparations Not only are the sulfonamides ineffective in such preparations but their use in any concentration represents a real danger to the user for three reasons (1) the substitution of an ineffective remedy for one which might be of value (2) the possibility now widely recognized of permitting the development of sulfonamide resistant organisms and (3) the development of cutaneous sensitization thus preventing the use of sulfonamides in serious conditions for which these drugs are known to be effective

These arguments may be supplemented by two additional statements (4) locally deposited sulfonamides retard healing and favor the formation of adhesions particularly in the peritoneal cavity and (5) where therapeutic results have seemingly been obtained (particularly following introduction of amounts as great as 5 gm into the peritoneal cavity after laparotomy) the efficacy of the antibiotic agent undoubtedly

resulted from postabsorptive action such as might have been more readily produced if the preparation were given orally or intravenously

Comparison with Other Topical Antibiotics As in the instance of the sulfonamides pharmaceutical manufacturers have attempted to broaden their listings of antibiotic preparations for local and topical application In the particular instance of penicillin dermal and oph thalmic ointments troches lozenges dental cones dusts for inhalation aerosols suppositories washes wet dressings and the like are mar keted (p 4452) similarly ointments and ophthalmic solutions of aureomycin are available as well as an ointment of streptomycin

Whereas many objections to the topical applications of sulfonamides do not apply to more recently introduced antibiotics there still remain deterrents to their popular use Exemplifying these principles peni cillin is bactericidal when applied locally or topically but it does possess a capacity for sensitization greater than when given parenter ally As many as 5 to 15 per cent of those to whom penicillin is locally applied develop contactual irritation due to sensitization This fact alone in our opinion suffices to eliminate for local and topical use those potent anti infective agents for which there may be later systemic indication in the treatment of more threatening bacterial invasion It is recommended therefore that those who think well of local and topical antibiotic therapy consider only those anti infective agents which are not useful systemically notably bacitracin (p 4247) and tyrothricin (p 4622) Perhaps the single justifiable exception to this tenet is the recommended use of aureomycin in ophthalmic solution (1 cc = 25 mg) because of its unparalleled efficacy in combating microbic invasions of the superficial tissues of the eye

Available Preparations for Systemic Use

There is available a bewildering variety of sulfonamide preparations for systemic use These include soluble and insoluble products and the sulfones separately considered in another place (p 4552)

Once again the practitioner is indebted to the Council on Pharmacy and Chemistry of the American Medical Association for elimination of many objectionable products

Soluble Sulfonamides Approved Council accepted soluble sulfona mides are sulfadiazine sulfamerazine and sulfapyrazine Elimination of the remaining soluble preparations (including sulfanilamide sul fapyridine sulfathiazole etc) is the result of their relatively increased toxicity as detailed previously in Table 11 (p 97)

THE SOLUBLE SULFONAMIDES

Product	Comment
Gantrisin (NU 445)	Newly introduced intestinal and urinary antiseptic (p 4625) See p 4340
Nisulfazole	A 10% suspension of paranitrosulfathiazole Used as retention enema in treatment of colitis Subject to same criticisms as other sulfonamides applied locally See text

THE SOLUBLE SULFONAMIDES *(Continued)*

Product	Comment
6257	A sulfonamide containing two molecules of sulfathiazole and three molecules of formaldehyde Not commercially available Under investigation for use in cholera (p 4284)
Sulamyd (Sulfacetimide) Tablets 0 5 gm (Schering)	Unofficial soluble sulfonamide favored by many urologists and gynecologists for urinary tract infections (p 4540)
Sulfadiazine U S P Tablets 0 5 gm (Abbott American, Buffington Cole Flint Eaton Harrower Lederle Lilly McNeil Merrell Miller Parke Davis Rorer Sharp & Dohme Smith Squibb Upjohn Vale Wyeth)	Well absorbed from gastro-intestinal tract, acetylated form very soluble well excreted by kidneys capable of effectual concentrations in blood and spinal fluid, over all high therapeutic efficacy with relatively low toxicity
Sodium Sulfadiazine U S P 5 gm vials of the sterile powder (Sharp & Dohme Squibb) Ampuls 10 cc of 25% (Lilly) Ampuls 50 cc of 5% (Sharp & Dohme)	For intravenous use for priming or loading dose do not exceed 100 mg per kilogram of body weight (approximately 40 to 45 mg per lb) up to a total dose of 5 gm preferably inject in 5% solution made up to volume with sterile distilled water
Sulfamerazine U S P (Sulfamethyldiazine) Tablets 0 5 gm (Abbott American Lederle Lilly Parke Davis Sharp & Dohme Squibb Upjohn)	Enjoys all therapeutic advantages of sulfadiazine but additionally maintains blood levels longer so that doses may be given at less frequent intervals
Sodium Sulfamerazine U S P Vials of 5 gm (Sharp & Dohme) Ampuls 10 cc of 25% (Lederle) Ampuls of 50 cc of 6% (Sharp & Dohme)	Obtain effective therapeutic levels by use of only 50 mg per kilo (approximately 20 to 25 mg per lb) as compared with double dose of sodium sulfadiazine make up in 5% solution with sterile distilled water or sterile isotonic saline for intravenous use
Sulfanilamide (Prontylin) U S P	Because of lesser toxicity prefer sulfadiazine sulfamerazine or sulfapyrazine No longer on approved list
Sulfapyrazine N N R Tablets 0 5 gm (Mead Johnson)	Comparable to sulfadiazine and sulfamerazine but less well established through later introduction and narrower experience
Sodium Sulfapyrazine Powder 5 gm (Mead Johnson)	Use as sodium sulfamerazine
Sulfapyridine	Because of lesser toxicity prefer sulfadiazine sulfamerazine or sulfapyrazine No longer on approved list
Sulfathiazole	Because of lesser toxicity prefer sulfadiazine sulfamerazine or sulfapyrazine No longer on approved list
Trisulfazine Tablets 0 5 gm N N R (Central)	Ingenious product combining 1 66 gm each of sulfadiazine sulfamerazine and sulfamethazine with sodium lactate Combination of partial doses of three soluble sulfonamides accomplishes cumulative antibiotic action with reduced incidence of cry talluria and urolithiasis (p 4541) addition of sodium lactate tends to favor solution of urinary crystals

Dosage Schedules Dosage schedules for soluble sulfonamides are more or less arbitrary The amount of priming and maintenance quantities depends for the most part on the severity of the infection and the relative size and age of the patient Determinations of blood and urine levels have almost completely gone out of vogue Practitioners now as always rely on clinical acumen to gauge therapeutic indications In general the rule of thumb is administration of sufficient antibiotic to lessen or completely ameliorate manifestations of microbic invasion without production of toxic manifestations

Using the sodium salt intravenously blood concentrations are quite clearly approximated through use of the following table

CALCULATION OF SULFONAMIDE BLOOD CONCENTRATIONS THROUGH INTRAVENOUS DOSAGES

Weight of Patient in Pounds	Weight of Patient in Kilos	Cubic Centimeters of 5% Solution of Sodium Salt to Raise Blood Level 1 mg %	Dose of Sodium Salt in Grams
11	5	1	0 05
22	10	2	0 1
33	15	3	0 15
44	20	4	0 2
55	25	5	0 25
66	30	6	0 3
77	35	7	0 35
88	40	8	0 4
110	50	10	0 5
132	60	12	0 6
154	70	14	0 7

Oral doses for the adult depend mostly on the severity of the infection In general the loading dose should be no less than 2 gm and no more than 6 gm preferably using tablets containing combined triple soluble salts with sodium lactate (trisulfazine) Maintenance doses depending on patient response and evidences of toxicity or sensitization average 0 5 to 1 gm every four hours day and night preferably given with alkaline fluids

For infants and children initial dose of soluble sulfonamide approximates 1 gm for each 20 pounds of body weight Maintenance doses approximate one quarter the loading dose given every four to six hours depending on clinical response

Antihistamines We favor simultaneous administration of antihistamine for prophylactic use against allergic hypersensitivities due to sulfonamide Antihistamines (p 4212) have no significant inherent toxicity though they may somewhat contribute to the drowsiness and ataxia resulting from antibiotic prevention of nuisance symptoms of acute histamine type hypersensitivity (p 4167) is of minor importance but mitigation of manifestations of tuberculin type hypersensitivity (p 4169) even in small part warrants the increased trouble and expense of concurrent prescription The practitioner may initiate therapy with daily doses of 200 mg of either of the original Council approved products pyribenzamine or benadryl (p 4214)

Insoluble Sulfonamides The Council on Pharmacy and Chemistry of the American Medical Association (1949) as in other instances has simplified the practitioner s problem by its decision to discontinue sul faguanidine from the list of approved insoluble sulfonamides However the two remaining approved products phthalylsulfathiazole and suc cinyl sulfathiazole have been challenged through introduction of thalamyd (phthalylsul facetimide)

INSOLUBLE SULFONAMIDES

Preparation and Manufacturer	Comment
Phthalylsulfathiazole (Sul fathalidine) N N R. Tablets 0 5 gm (Sharp & Dohme)	(See Table 12 p 191) Official insoluble sulfonamide average daily adult dose 4 to 8 gm given in four divided portions Average loading dose preliminary to intestinal surgery 6 to 8 gm followed by similar amount for total daily dose in four divided portions for three to five days prior to operation and at least an equal amount of time postoperatively
Succinylsulfathiazole (Sul fasuxidine) Tablets 0 5 gm (Sharp & Dohme) Cremosuxidine 30 cc = 3 gm	*Official insoluble sulfonamide less favored than phthalyl sulfathiazole (Table 12 p 191) since larger dosages are required for equivalent effect (250 mg per kg)*
Sulfaguanidine	No longer Council accepted
Thalamyd (Schering)	Newly introduced product midway between soluble and unsoluble products (p 4569)

BACTERIAL SPECTRUM OF SULFONAMIDES

Staphylococcus

Organism sulfonamide sensitive but may develop resistance prefer penicillin supplemented, if necessary with aureomycin or chloramphenicol *reserve* streptomycin for third choice use sulfonamide only in the greatest need

Streptococcus

Most strains sulfonamide sensitive however anaerobes are resistant and other varieties may develop fastness *liability of streptococcus to produce tuber culin type hypersensitivity (as in rheumatic fever)* sharply limits use of sulfona mide which may produce similar pathological disturbances as the result of drug hypersensitivity prefer penicillin with supplementation by aureomycin and chloramphenicol reserve streptomycin for third choice use sulfonamide only in desperation

Pneumococcus

Organism sulfonamide sensitive but prefer penicillin on grounds of lesser toxicity if supplementation is required chose aureomycin or chloramphenicol with sulfonamide as third choice

Meningococcus

Organism sulfonamide sensitive many clinicians regard *sulfonamide as first* choice in view of gravity of infection use combined sulfonamide penicillin *attack, reserving aureomycin and chloramphenicol for third choices*

Gonococcus

Organism sulfonamide sensitive but often develops bacterial resistance pre fer penicillin on rare occasion when supplementary therapy is needed choose aureomycin chloramphenicol or streptomycin

BACTERIAL SPECTRUM OF SULFONAMIDES (*Continued*)

Typhoid Bacillus

E typhosa somewhat sulfonamide sensitive not comparable to chloramphenicol which is preparation of choice

Salmonellae (Paratyphoid)

Salmonellae somewhat sulfonamide sensitive but not comparable to chloram phenicol which is preparation of choice

Shigellae

(Bacillary Dysentery)

Shigellae somewhat sulfonamide sensitive but not comparable to chloram phenicol and aureomycin which are preparations of choice

Colon Bacillus

Organism somewhat sulfonamide sensitive but not comparable to aureomycin and chloramphenicol which are preparations of choice with streptomycin for supplementation

Cholera

V comma somewhat sulfonamide ensitive excellent results reported con tinue use of soluble sulfonamide or of thalamyd until status of aureomycin and chloramphenicol is more clearly defined

Tuberculosis

M tuberculo is somewhat sulfonamide sensitive but not comparable to strep tomycins which are preparations of choice

Leprosy

Organism somewhat sulfonamide sensitive but not comparable to sulfones which are preparations of choice

B anthracis

Organism somewhat sulfonamide sensitive prefer penicillin and use sul fonamide as desperation supplementation

H influenzae

Organism somewhat sulfonamide sensitive particularly in conjunction with streptomycin, however not comparable to aureomycin and chloramphenicol which are preparations of choice

Chancroid

H Ducreyi is sulfonamide sensitive but not comparable to aureomycin and chloramphenicol which are preparations of choice

Brucellosis

Br melitensis somewhat sulfonamide sensitive particularly in conjunction with streptomycin not comparable to aureomycin and chloramphenicol which are preparations of choice

Plague

P pestis somewhat sulfonamide sensitive excellent results reported, continue use until status of aureomycin and chloramphenicol can be more clearly defined

Glanders

M mallei is generally re istant sulfonamide therapy may be tried as a des peration remedy

Trachoma

Virus somewhat sulfonam de sensitive but not comparable with aureomycin and chloramphenicol which are preparations of choice

BACTERIAL SPECTRUM OF SULFONAMIDES (*Continued*)

Follicular Conjunctivitis

Virus somewhat sulfonamide sensitive but not comparable with aureomycin and chloramphenicol which are preparations of choice

Lymphogranuloma Venereum

Virus somewhat sulfonamide ensitive but not comparable with aureomycin and chloramphenicol which are preparations of choice

Molluscum Contagiosum

Virus somewhat sulfonamide sensitive but not comparable with aureomycin and chloramphenicol, which are preparations of choice

Actinomycosis

Fungus somewhat sulfonamide sensitive continue to use with penicillin as desperation remedy

Rheumatic Fever

If hypersensitivity theory of pathogenesis is accepted substitute penicillin for prophylaxis and treatment of Phase 1 avoid sulfonamide because of hyper allergenicity

Rheumatoid Arthritis

If hypersensitivity hypothesis is accepted (p 4169) consider sulfonamides contraindicated

Urinary Infections

Most gram negative bacilli sulfonamide sensitive prefer aureomycin or chlor amphenicol reserving streptomycin for supplementation if necessary

Antibiotic Synergism

Concurrent empiric use of two or more antibiotics often is dictated by necessity as in Probatory and Desperation Anti infective Therapy (p 4219) However there are times when combinations are scientifically employed on the basis of demonstrable synergism

Sulfonamide Penicillin Definitively greater bacteriostatic effects are noted when sulfadiazine and penicillin are used in combination against certain strains of streptococci and staphylococci The synergistic action of penicillin and sulfonamide is due to the fact that penicillin acts predominantly at the time of cell division whereas sulfadiazine reduces the rate of multiplication of organisms

Sulfonamide Streptomycin Sulfonamide streptomycin synergism also has been demonstrated clinically in the treatment of brucellosis tula remia and H influenzae meningitis Particularly in acute brucellosis neither streptomycin nor sulfonamide alone appeared to accomplish much therapeutically It was not until combined therapy was inaugu rated that undeniably specific results were obtained Unfortunately this therapeutic triumph enjoyed a relatively brief period of popularity since it was no sooner demonstrated than the even more sensational results of aureomycin and chloramphenicol therapy relegated syner gistic treatment by sulfonamide and streptomycin to the growing list of worthy but obsolescent achievements

Desperation Antibiotic Therapy Those purists who frown on com bined antibiotic therapy may be reminded of these demonstrable

synergisms when the realistic practitioner faced with problems of overwhelming infections inadequate responses remissions relapses exacerbations and complications prepares to throw the book in his efforts to salvage the hard pressed patient

Sulfonamide Antagonisms

It is generally accepted that the major effect of sulfonamides is prevention of synthesis by bacteria of pteroyl compounds which in turn are derivatives of para aminobenzoic acid and hence related to folic acid Pteroyl compounds are required as growth factors by many species To be efficacious sulfonamide therapy must be administered in doses sufficient to prevent utilization of available para aminobenzoic acid In turn para aminobenzoic acid is capable of antisulfonamide action

The practical significance of sulfonamide para aminobenzoic acid antagonism has been emphasized by the growing popularity of procaine penicillin salts Inasmuch as para aminobenzoic acid is a degradation product of procaine procaine penicillin may alter sulfonamide activity and vice versa Fortunately preliminary reports suggest that the interference is negligible (J A M A 140 1068 1949)

Therapeutics

As previously detailed it is only in the rare instance that sulfonamide remains the prime preparation of choice in the prophylaxis or active treatment of microbic invasions For the most part it has assumed secondary or even te tiary importance when less toxic remedies fail or when the gravity of the invasion requires combined treatment as a desperation ge ture

Prophylaxis

Staphylococcal Infection prefer penicillin

Streptococcal Infection prefer penicillin Consider sulfonamides contraindicated if hypersensitivity phenomena are feared as in rheumatic fever

Meningococcal Infection consider use for mass prophylaxis in epidemics

Gonorrhea unsatisfactory since resistant strains may develop prefer penicillin which is equally active against sulfonamide sensitive and sulfonamide resistant strains

Colon Bacillus Infections used by urologists as sulamyd to prevent bladder infections consequent to instrumentation Prefer aureomycin chloramphenicol or streptomycin

Cholera Use soluble preparations for mass prophylaxis in epidemics

Chancroid effectual prophylaxis particularly in army encampments Single doses of 2 gm on leaving and returning to barracks protect against gonorrhea and chancroid

Shigellosis (Bacillary Dysentery) use soluble sulfonamide for mass prophylaxis during epidemic

Surgery use insoluble sulfonamides preparatory to gastric intestinal or urinary tract procedures

Specific Anti Infective Therapy

Staphylococcemia in conjunction with penicillin and aureomycin or chloramphenicol
Meningococcemia many regard soluble sulfonamide as first choice with supplementation by penicillin
Cholera regard as first choice until status of aureomycin and chloramphenicol is established
Glanders try as desperation remedy
Actinomycosis try as desperation remedy
Torulosis try as desperation remedy

SULFONES

The sulfones have as their parent radical diamino-diphenyl sulfone In the body it is most likely that each breaks down to the parent radical which then functions as the active principle

Pharmacology

The sulfones are rapidly absorbed and achieve good blood concentration which unfortunately cannot be maintained through rapidity of renal excretion

SULFONES

Preparation	Route	Initial Dose	Optimum Dose	Course	Intermission	Toxicity
Promin (p 4481)	*Intra venous*	1 gm	*5 gm*	2 wks	*1 wk*	*Anemia* leukopenia allergic dermatitis
Diasone (p 4300)	Oral	0 3 gm with 10% Sodium Bicarbonate	0 9 gm *daily*	2 mos	2 wks	Anemia leukopenia nausea vomiting hematuria drug fever *Herxheimer* reaction
Promizole (p 4482)	Oral	0 5 gm t i d p c	6-8 gm daily	2 mos	2 wks	As above but rare
Sulphetrone Experimental Use Only (p 4553)						

Therapeutics

The sulfones appear to be most efficacious in the treatment of leprosy In combination with streptomycin they may prove useful in tuberculosis

Toxicity

The sulfones are toxic to erythrocytes and usually produce an anemia of greater or lesser severity Repeated blood counts are mandatory in the control of therapy Less frequently leukopenia and agranulocytosis are encountered

Oral products especially may cause nau_ea vomiting and gastric irritation lessened and mitigated by u e of sodium bicarbonate Allergic forms of dermatitis drug fevers (p 24) and intensification of rashes as in the syphilitic Herxheimer reaction (p 3281) are encountered with all products Urine specimens must be examined every few days for evidences of renal irritation (hematuria albuminuria) Toxic symptoms abate rapidly though anemia may require administrations of iron liver extract and/or whole blood transfusion Promizole seems least toxic (p 4386)

SULPHETRONE

Sulphetrone is presently available for experimental use only Its chemical formula is 4 4 bis(gamma phenyl N propylamino-diphenyl sulfone tetra odium sulfonate) It is being tried experimentally in human tuberculosis (Lancet 2 144 1948 J A M A 139 62 1949)

Sulphetrone has no acute toxicity but chronic untoward manifestations include hemolysis leading to secondary anemia and goiterogenesis Until these latter can be eliminated it is unlikely that sulphetrone will be distributed for use in general practice

SURAMIN SODIUM U S.P

[Naphuride Germanin Fourneau 309 Antryptol Bayer 205]

Suramin is a urea derivative (Hexa sodium bis (m aminobenzoyl m amino-p methylbenzolyl l naphthyl amino 4 6 8-trisulfonate carbamide) with potent trypanocidal activity

Available Products

Naphuride Sodium U S P 1 gm ampuls (Winthrop) Sprinkle powder on surface of diluent to avoid clumping Use at once

Therapeutics

An effective relatively non toxic trypanosomicide used in African sleeping sickness both gambesian and rhodesian (p 533)

For prophylaxis inject intravenously 1 gm in 10% sterile distilled water Repeat once a week for two doses and then at intervals of three months

For active treatment give an initial probatory dose of 0 3 gm If there are no untoward reactions inject 1 gm in 10% sterile distilled water intravenously or intramuscularly once weekly for five to ten weeks In severe illness the first three doses may be injected on alternate days (p 4594)

Toxicity

Albuminuria hematuria cylindruria hemolysis (in large doses) toxicoderms (p 24) chills fever headache nausea and pruritus Rarely conjunctivitis stomatitis purpura and agranulocytosis

Avoid with renal insufficiency (p 2275)

SYPHILIS

[Lues]

Principles of Diagnosis and Therapy

1 Most expert discussions of syphilis are so unnecessarily complicated and obtuse that the practitioner may welcome a simplified restatement of Principles of Diagnosis and Therapy

2 During life the definitive laboratory diagnosis of syphilis is *established only by darkfield demonstration of spirochetes (Fig 7 p 46)* in secretion obtained from the chancre (Fig 48 p 335) or a secondary lesion (Fig 49A B C D E F p 338)

3 Serologic tests for syphilis are notoriously unsatisfactory They are consistently negative in the highly infectious primary stage of the disease and at any time may give false positive responses to at least fifty eight recognized non syphilitic factors To the published list of disturbances giving the false positive serologic test for syphilis (p 337) Stokes recently added streptococcal infections pemphigus and subacute bacterial endocarditis

4 The biologically false positive serologic test causes confusion in many ways Interpreted as indicative of syphilis patients are unwittingly stigmatized and unnecessarily treated Additionally the syphilitic who has a biologic false positive test may be considered serologically resistant Under this latter circumstance initial treatments are regarded as unsatisfactory and repeated or continued therapy is recommended to the detriment alike of statistical considerations and patient comfort

5 The practitioner s safest check against misinterpretation of serologic tests for syphilis is a request for a battery of reactions as performed by the Venereal Disease Research Laboratory of the U S Public Health Service (Kolmer Kahn Klein Mazzini Hinton) Perhaps the best warning of a non specific positive result is serologic discord in which certain tests are negative or feebly positive while others are positive in higher dilutions

6 Given a report which is positive across the board the practitioner need have no feeling of insecurity concerning the laboratory diagnosis However the fact that the patient carries a positive test does not mean necessarily that presenting symptoms and signs are syphilitic in origin Interpretation of laboratory findings remains the province of the clinician and decisions often challenge his keenest acumen

7 The previous statement that irrespective of the stage of syphilis the practitioner owes it to himself and to his patient to collect cerebro spinal fluid for a complete examination (p 339) cannot be too strongly

emphasized Knowledge that the spinal fluid is positive before institution of therapy assists the practitioner in the arrangement of his therapeutic program and also serves as a protection to him in the event that his judgment later is criticized In the presence of abnormalities of the fluid the patient is given a more guarded prognosis and the necessity for retreatment and prolonged observation is accentuated

8 It is customary to subdivide clinical manifestations of syphilis into various stages which include primary seronegative primary seropositive secondary early latent late latent asymptomatic neurosyphilis tertiary syphilis neuro syphilis and cardiovascular visceral pre natal and pregnancy infections (Table 22 p 336) We regard these artificial classifications as misleading and inaccurate The high percentage of patients who show positive cerebrospinal fluid findings in early stages of infectious syphilis illustrates the fact that the spirochete is widely disseminated from the start of infection Presentation of different treatment schedules for each stage of syphilis produces confusion that is not justified by results obtained It is for this reason that we favor a single treatment schedule for all stages and phases of syphilis with certain minor variations later described in detail

9 Treponema pallidum is sensitive to penicillin aureomycin chloramphenicol streptomycin and arsenicals

On all counts penicillin is the antibiotic of choice in the treatment of all tages of syphilitic infection Given in adequate dosage for a sufficiently long period of time and repeated at least once under any circumstances the percentage of cures exceeds even those obtained by mas ive chemotherapy by the intravenous drip method (five day treatment p 344) Against the latter s significant toxicity (approximating 1 per cent) and its treatment mortality (approximating 0 25 per cent) penicillin therapy of syphilis has negligible untoward reactions and no mortality whatsoever

10 Despite the fact that the hazards of arsenic toxicity have been greatly lessened through introduction of the antidote BAL (p 4251) we favor unmodified and uncomplicated penicillin therapy for the original treatment and for first retreatment of all patients with syphilis irrespective of the stage of the disease It is quite likely that aureomycin or chloramphenicol may replace arsenicals as second choices since both products are without significant toxic reactions and are efficacious when given orally

11 Until experts have definitively demonstrated significant advantages when penicillin and/or aureomycin chloramphenicol are supplemented by arsenicals in the treatment of syphilis it is our opinion that the practitioner should reserve the hazardous therapeutic agent for use in the rare patient who is sensitive to the newer antibiotics or who shows clinical or serologic resistance following initial treatment and one course of retreatment

12 As a spirocheticidal agent bismuth is so feeble as compared to newer products that it does not merit consideration except for possible prevention of the controversial Herxheimer reaction preliminary to treatment of cardiovascular and advanced neurologic infections

Completely obsolete as antisyphilitic drugs are trivalent arsenicals other than mapharsen and clorarsen pentavalent arsenicals and particularly tryparsamide mercurials and combinations of arsenic and bismuth

13 The importance of naturally acquired active immunity to syphilis originally demonstrated by Bruusgaard (p 333) has been strikingly confirmed at the Yale University School of Medicine (Rosahn J Ven Dis Inf 27 293 1946) The Yale figures based on the spontaneous course of untreated syphilis check very closely with Bruusgaard s statistics In the latter the total of spontaneous cures and asymptomatic latency with positive serology approximated two thirds of those who had been originally infected (p 340) Rosahn found that only 38 9 per cent of 198 autopsied patients who had received no treatment for their disease presented any anatomic changes at autopsy consistent with the diagnosis of syphilis and the majority of the 198 patients (121 or 61 1 per cent) presented no evidence at autopsy of tissue alteration suggestive of syphilitic disease

14 So important are Rosahn s findings that his general conclusions are worthy of restatement in his own words If it is assumed that our findings represent a fairly accurate summary of the end results of untreated syphilis it can be concluded that had treatment been administered adequately and early to the entire group it could not possibly have effectively altered the course of the disease in more than 4 out of 10 patients since 6 out of 10 untreated patients died with no evidence of syphilis at autopsy On closer inspection even this ratio of 4 out of 10 patients who could have benefited by treatment is excessive because only a little more than 2 out of the 10 actually died as a result of syphilis The remaining 8 out of 10 patients with syphilis all succumbed to an unrelated disease process and the fact that some of them had developed a syphilitic lesion or a positive serologic test for syphilis was apparently of no great significance Treatment of the whole group could then have possibly altered the end results in only the two who actually died of syphilis out of ten untreated cases

15 The participation of allergic hypersensitivity in syphilitic manifestations remains incompletely evaluated Hypersensitive tissue reactions might well explain lesions in which demonstration of spirochetes is difficult or nearly impossible as exemplified by tabes dorsalis paresis and gumma (pp 1963 2465 2938 and Figs 49 G and H p 338) Furthermore the immune bodies that produce serologic tests for syphilis absent during infectious phases of the disease and only demonstrable after an incubation period approximating three weeks to three months may measure hypersensitivity rather than infectivity

Practical Management

Prophylaxis

1 Except for prenatal infections syphilis is almost always a venereal disease Previously recommended measures for venereal prophylaxis (p 3122) are woefully inadequate they do not prevent extragenital

transmi sion of the disease as for example by kissing they are not efficacious against venereal disease of virus origin (lymphopathia venereum) or those cau ed by H ducreyi (chancroid) or donovani (granuloma inguinale)

2 The importance of venereal prophylaxis is such that intensive and combined antibiotic therapy is warranted for the prevention of all five venereal diseases To accomplish this in syphilis and gonorrhea it is probably necessary only to inject intramuscularly 300 000 units of crystalline procaine penicillin G and to pre cribe concurrently for the remaining infections capsules of aureomycin or chloramphenicol in daily doses of 2 to 4 gm for three to five days

3 Despite a high percentage of successful results obtainable by minimum doses the practitioner cannot content him elf with anything less than an unblemished prophylactic rate In point of fact the incon venience and expense of overtreatment additionally may erve to dis courage the patient from frequent exposure

4 It is our personal opinion that the exposed patient should receive no less than 6 million units of cry talline procaine penicillin G in aqueous suspension given over a period of ten days This can be accomplished by injecting intramuscularly 600 000 units daily sub stituting the preparation in oil with 2% aluminum monostearate before the intervening Sunday or holiday Concurrently to prevent penicillin resistant diseases we favor oral administration of 2 to 4 gm of aureo mycin or chloramphenicol given in 4 divided doses for at least three to five days

5 During antibiotic therapy and for two weeks thereafter pre scribe 200 mg of antihistamine daily to prevent hypersensitivity reac tions to invading microbe or therapeutic antigen

6 In addition to preliminary physical examination and erologic testing the patient must return at monthly intervals for at least six visits for repetition of tests Only then if all is well can complete assurance as to the success of prophylactic therapy be given (p 347)

Immediate Care

1 Before institution of therapy do a complete physical examination draw blood for performance of a battery of serologic tests obtain cerebrospinal fluid and subject it to the same tests used on serum get an x ray of the chest for determination of pre treatment appearance and size of heart and aorta make a neurologic survey (p 1402) and order an electrocardiogram

2 If the diagnosis of yphilis rests completely on serologic tests look for the presence of other diseases capable of giving false positive reactions (p 337) Be particularly wary when there is serologic dis cord with negative re ponses to some tests and low titers in others the more especially if a reliable patient denies sexual exposure

3 In the presence of advanced cardiovascular or neurologic lesions precede penicillin therapy with 6 to 10 weekly intramuscular injections of 2 cc of insoluble bismuth subsalicylate in oil (p 4255)

4 Under all other circumstances immediately institute intensive penicillin therapy Deposit intramuscularly 600 000 units of crystalline procaine penicillin G in aqueous suspension Repeat injections daily for a minimum period of fifteen days to total 9 million units Before the intervening Sunday or holiday substitute the oil suspension with 2% aluminum monostearate Make up the total of 9 million units by an added injection of aqueous suspension on the sixteenth day

5 Concurrently with penicillin and for a period of two weeks afte the last dose give 200 mg daily of antihistamine using pyribenzamine or benadryl

6 Inasmuch as other venereal diseases have a much shorter period of incubation than syphilis it is not necessary to give concurrent prophylactic treatment to the patient with active infection unless there has been repeated exposure after acquisition of luetic disease

7 Should it be necessary to protect concurrently against the venereal diseases not affected by penicillin (chancroid lymphopathia venereum and granuloma inguinale) or should it be thought advisable to supplement penicillin therapy with another potent antibiotic prescribe oral doses of aureomycin or chloramphenicol Order 4 to 6 gm daily in 4 divided doses for the fifteen day period during which deposits of penicillin are being made

Continuing Care (Favorable Course)

1 Have the patient report at weekly intervals for three months following initiation of therapy At each visit repeat physical survey and serologic tests

2 Whether or not the patient has clinical or serologic evidences of relapse (p 347) recommend a second course of therapy three months after the first course has been completed

3 Continue monthly observations after termination of the second course for an additional six months If the criteria of cure (p 347) are met no further therapy is required but the patient is advised to report annually for a five year period

Continuing Care (Unfavorable Course)

1 For the patient with penicillin sensitivity the practitioner has his choice of oral treatment with aureomycin or chloramphenicol or a course of ambulatory conservative treatment as advised by the cooperative clinical group using mapharsen and bismuth (Table 23 p 345)

2 For aureomycin therapy O Leary (Mayo Clinics 1948) used doses of 500 mg every four hours for 5 days 750 mg every four hours on the fifth and seventh days and 500 mg every four hours thereafter until a total of 44 2 gm had been taken With this program untoward reactions included nausea and vomiting but darkfield examinations were negative within sixteen hours and all primary lesions were completely healed by the end of the treatment period Despite these favorable responses it is our opinion that the private patient should receive larger doses (4 to 6 gm daily) for a longer period of time (15 days)

3 As a substitute for aureomycin in those patients who have gastric

intolerance to the antibiotic the method of Romanowsky using chloram phenicol may be tried Romanowsky gave total daily doses of 30 to 120 mg per kilogram of body weight per day (2 1 to 8 4 gm for the average adult weighing 150 lbs) Six divided doses were prescribed at approximately 4 hour intervals over a period of four to eight days Again we favor the larger doses (at least 6 gm) for a longer period of time (15 days)

4 In addition to arsenotherapy for the penicillin sensitive maphar en or clorarsen injections must be considered for patients who fail to fulfill the criteria of the cure (p 347) and who manifest evidences of treatment failure (p 347) following original treatment and one re treatment course of penicillin and/or aureomycin chloramphenicol

5 Before recourse to ar enotherapy look for the presence of other factors capable of giving false positive serologic tests remembering that these disturbances may afflict the syphilitic as well as the non syphilitic (p 337) Additionally it is necessary to weigh the hazards of therapy against the chances for spontaneous cure as discussed previously

6 For re treatment of unfavorable cases the routine employed by the New York City Health Department is recommended The peni cillin course as previously detailed is repeated At its termination the patient is given bi weekly intravenous injections of 40 to 60 mg of maphar en or clorar en to total 20 injections Concurrently intra muscular deposits of 2 cc of insoluble bismuth subsalicylate in oil are made once weekly for the 10 week period

7 During arsenotherapy frequent physical examinations and analy ses of blood and urine are required for early detection of evidences of toxicity If such develop treatment is interrupted and intramuscular injections of BAL are begun (p 4251)

8 Despite contrary opinions from certain experienced syphilolo gists main reliance may be placed on penicillin in the management of advanced or resistant infections of the nervous system There is no reliable proof that supplementary intrathecal instillations or hyper thermia (by malarial infection or electrically induced fever) warrant attendant inconveniences and hazards Dattner a pioneer in malarial therapy asserts that there is almost unanimous agreement among experts that the intrathecal injection of penicillin is unnecessary and even dangerous The same author also states that the results obtained (with intramuscular deposits of penicillin) are similar to or better than those following malarial therapy (J A M A 141 1260 1949)

TEGUMENTARY SYSTEM NEOPLASMS OF

The practitioner encounters neoplasms of the skin as part of his every day experience The vast majority of these are benign (pp 3199–3209 Figs 911–916 p 3200 and Figs 917–920 p 3201) and require only excision or electrocoagulation for cosmetic rea ons

Pre cancero.es and actual malignancies (pp 3209–3227) also occur with great frequency (Table *below*) Attention is drawn to them by the appcarance of nodules cysts and tumors (p 3210) or fissures cracks clefts rhagades and ulcers of the skin (p 3218) Treatment of the potential or veritable skin malignancy may require consultation with dermatologist surgeon or roentgen therapist

PRE CANCEROSES AND MALIGNANCIES OF THE TEGUMENTARY SYSTEM

Lesion	Illustration	Page Reference
Pigmented moles	Fig 916 p 3200	p 3204
Blue naevi		p 3205
Senile sebaceous aderomas		p 3205
Fibromas		p 3206
Multiple neurofibromatosis (von Recklinghausen s disease)	Fig 918 p 3201	p 3206
Multiple benign cystic epi theliomas		p 3208
Cerebriform mole		p 3205
Sebaceous cysts		p 3208
Syringocystomas		p 3209
Malignancies due to me chanical trauma		p 3212
Leukoplakia	Fig 921 p 3201	p 3218
Chronic radiodermatitis	Fig 898, p 3160	p 3179
Chronic infective ulcers		p 3215
Occupational keratoses		p 3216
Arsenical keratoses		p 3216
Senile keratoses	Fig 922 p 3201	p 3216
Seborrheal keratoses	Fig 922 p 3201	p 3216
Seborrheal keratoses (senile warts)		p 3217
Cutaneous warts		p 3217
Basal cell epitheliomas (ro dent ulcers)	Fig 923 p 3220	p 3220
Squamous cell epithelioma (prickle cell epithelioma)	Fig 924 p 3220	p 3223
Paget s disease of the breast		p 3223
Bowen s disease	Fig 925 p 3221	p 3225
Melanocarcinoma	Figs 926 and 927 p 3221	p 3225
Sarcomas		p 3226
Idiopathic multiple hemor rhagic sarcomas (Ka posi s disease)	Figs 928 and 929 p 3221	p 3226
Metastatic carcinomas		p 3227
Lymphosarcoma	Fig 930 p 3221	p 3227
Mycosis fungoides (granu loma fungoides)	Figs 992 and 993 p 3385	p 3380

Practical Management

1 If the lesion is single isolated and situated in a non strategic area (thoracic wall abdominal wall or back) excise widely under local anesthesia (p 3935) Try to go at least one half inch beyond the lesion in all directions Remove a segment at least one half inch in depth

Send specimen to pathologist for histologic examination Consider x ray therapy if lesion recurs or pathologist reports that malignant cells extended to or beyond line of incision

2 Pre cancerous or actually malignant lesions of strategic areas such as the nose lip cheek or eyelid require reference to the con sulting dermatologist It is his decision to weigh advantages of biopsy against hazards He must also decide whether therapy is to be con ducted by surgical excision or irradiation If a choice is afforded elect excision which permits histologic examination and which may be followed by irradiation therapy if necessary

3 If the local lesion is no longer isolated and there are metastatic glands patient must be hospitalized and prepared for a wide block dis ection followed by intensive radiation therapy

4 In the presence of multiple skin malignancies it may be necessary to consider desperation remedies such as injection of nitrogen mustard (p 4439) or use of radioactive isotopes such as P^{32} (p 605)

TENIASIS

[Tapeworm Infestations Cestodiasis]

Principles of Diagnosis and Therapy

1 Tapeworm infestations usually result from ingestion of improperly prepared fish beef or pork (Fig 435 p 1900)

2 Establish diagnosis by identification of segments or ova in feces (Fig 1099 p 3730)

3 Except in rare instances tapeworm infestations do not cause sys temic manifestations although a severe hyperchromic macrocytic anemia may accompany Bothriocephalus infestations (p 1083)

4 Treatment of tapeworm infestations has been made considerably more satisfactory through transduodenal introduction of anthelmintics and through increasing recognition of efficacy of quinacrine (atabrine) and hexylresorcinol (caprokol) With oleoresin of aspidium these have replaced more toxic carbon tetrachloride and pelletierine

Practical Management

1 Order low residue diet for twenty four or forty eight hours prior to administration of anthelmintic

2 On eve of therapy prescribe 30 to 45 gm of sodium sulfate with 2 glasses of warm fluid

3 On morning of treatment pass duodenal tube Do not administer drug until alkaline bile stained material has been aspirated

4 For anthelmintic of choice give 0 6 to 1 0 gm of quinacrine hydrochloride (atabrine) U S P Improvise a solution by pulverizing and dissolving 6 to 10 tablets each of 0 1 gm dosage (Winthrop) If the duodenal tube is not used give 3 tablets every fifteen minutes for three doses with large quantity of fluid

5 For second choice prepare a fresh mixture of oleoresin of aspidium To 8 gm of anthelmintic add 30 gm of sodium sulfate 30 cc of mucilage of acacia and sufficient water to make 100 cc

6 For third choice give 1 to 3 gm of hexylresorcinol available in gelatin coated capsules each containing 0 2 gm (Sharp & Dohme) If taken orally caution patient to swallow whole If instilled transduodenally remove outer capsule and suspend contents in 30 cc of mucilage of acacia and 70 cc of water

7 Whichever anthelmintic is used flush duodenal tube a few moments after drug has been introduced and then quickly withdraw

8 Two hours after introduction of anthelmintic repeat saline purge using 30 to 45 gm of sodium sulfate If there has been no bowel evacuation after another two hours initiate movement with soapsuds enema

9 Examine all stools and enema returns for two days searching for scolex (Fig 435 p 1900)

10 After six weeks if scolex has not been identified and ova or segments are still present in stools repeat therapy using same or alternate anthelmintic

TERRAMYCIN

Terramycin a product with potent antimicrobic activity is produced by growth of the mold Streptomyces rimosus A crystalline amphoteric substance terramycin is highly stable and can be reacted chemically with certain acids and bases to form crystalline salts In the dry crystalline state terramycin and its salts are highly stable at 25° C They maintain their potency for a period of twelve months when stored at room temperature

Available Preparations

Terramycin (Pfizer) Capsules containing 250 mg

Absorption and Excretion

Terramycin is rapidly absorbed following parenteral or oral administration It is excreted in a biologically active form primarily in urine Given orally to fasting subjects in single doses of 25 to 50 mg per kg of body weight peak serum concentrations are produced after two to four hours Average maximum serum concentrations approximate 18 micrograms per ml and average urinary excretion is 37 per cent of the total dose Serum levels remain at a plateau for two to four hours and then decline

Toxicity

Terramycin is relatively non toxic as indicated by acute and chronic studies in experimental animals and man Human patients have received

oral daily doses of 5 gm of terramycin hydrochloride for one month without significant untoward reactions

In a few patients mild gastrointestinal disturbances glossitis looseness of stools mild nausea and vomiting are encountered Reduction in side effects is accomplished by administering capsules after meals Allergic reactions have not been seen

Bacterial Spectrum (p 4243)

Terramycin has a broad bacterial spectrum It is effective both in the test tube and in the living animal against gram positive cocci and bacilli gram negative cocci and bacilli (aerobic and anaerobic) rickettsia and certain viruses In the treatment of mild infections the recommended daily dose is 2 to 3 gm in 4 divided amounts given at 6 hour intervals In severer infections double quantities may be employed provided that toxic manifestations do not sooner develop

Therapeutics

Thus far terramycin therapy has proven succes ful in the management of acute pneumococcal pneumonias pneumococcal peritonitis bacterial pneumonias due to Staphylococcus aureus Streptococcus hemolyticus and Streptococcus viridans hemolytic and non hemolytic streptococcal invasions including acute follicular tonsillitis septic sore throat erysipelas cellulitis abscesses subacute bacterial endocarditis chronic pyelonephritis and other urinary tract infections localized staphylococcal infections and urinary tract invasion staphylococcal sepsis and endocarditis gonorrheal urethritis anthrax hemophilus influenzal invasions whooping cough acute brucellosis urinary tract infections due to E coli and A aerogenes re piratory infections due to K pneumoniae (Friedlander bacillus) tularemia and the rickettsial diseases including typhus fever tsutsugamushi fever Rocky Mountain spotted fever Q fever and rickettsialpox

Preliminary data also suggest that a single dose of 60 mg per kilogram of body weight eliminates Treponema pallidum from the dark field in infectious syphilis Of the virus and viral like infections succe sful clinical results have been obtained in atypical pneumonitis herpes zoster lymphopathia venereum granuloma inguinale and perhaps influenza virus AB

Terramycin has been disappointing in the treatment of typhoid fever urinary infections due to Ps pyocyaneus most cases of salmonellosis measles mumps malaria variola trichinosis and amebiasis

Comparison with Other Antibiotics

From what has been stated above it is clear that terramycin duplicates the remarkable antibacterial proclivities of penicillin and aureomycin or chloramphenicol Since there has been greater experience with antibiotics previously introduced terramycin probably will be employed mostly in the management of infections resistant to older preparations and in the treatment of the rare patient intolerant of penicillin aureomycin and/or chloramphenicol

TETANUS

[Lockjaw]

Principles of Diagnosis and Therapy

1 Tetanus is a preventable disease In the military service compulsory active immunizations with tetanus toxoid virtually eliminated morbidity and mortality In civilian life similar measures are of equal importance particularly in farm and rural areas where most wounds are contaminated by Clostridia (p 294)

2 Passive immunization is available for those who have not had previous protection and who have suffered a possibly contaminated wound By transfer of antibody preformed in the experimental animal (horses cattle) immediate protection is afforded during the lag period between injection of toxoid and development of an effectual titer of antibody Unfortunately passive immunization exposes the patient to hypersensitivity phenomena and must be preceded by ophthalmic and skin testing for hypersensitivity by desensitization where necessary and by concurrent and continued administration of antihistamines (p 4187)

3 Early active treatment with tetanus antitoxin is reasonably effective in the neutralization of free toxin However delayed therapy produces progressively diminishing results since toxin becomes fixed by nerve tissues where it is inaccessible to neutralization by antitoxin

4 Clostridium tetani is somewhat penicillin sensitive The antibiotic however has no antitoxic action and hence is relatively ineffectual as a specific once neuromuscular manifestations have been established

5 In the treatment of active tetanus the practitioner is faced with a dual problem It is necessary to control by pharmacologic agents neuromuscular manifestations meanwhile maintaining a clear airway by mechanical means Since most of the available neuromuscular relaxants and antispasmodics are also respiratory depressants patient management offers a formidable challenge to the practitioner who will require full time observation of shifting problems preferably in association with a competent nursing staff and consultants

Practical Management

Prophylaxis

1 Advocate triple active immunization for infants children and adults who did not serve in World Wars I or II and who have no history of previous protection Preferably use diphtheria toxoid alum precipitated tetanus toxoid alum precipitated pertussis vaccine combined U S P (National Drug Sharp & Dohme Squibb Lederle) To youngsters give three subcutaneous injections preferably at insertion of deltoid each of 0 5 cc at intervals of three to four weeks For adult second and third injections increase the dose to 1 cc

2 For the adult who has had pertussis prefer diphtheria and tetanus

toxoids alum precipitated U S P (National Drug Parke Davis Pitman Moore Sharp & Dohme Squibb Wyeth) Inject subcutaneously at insertion of deltoid two doses each of 1 cc at an interval of four to six weeks

3 For the adult who has had both pertussis and diphtheria or who is Schick negative prefer tetanus toxoid alum precipitated U S P (Lederle Lilly National Drug Parke Davis Pitman Moore Sharp & Dohme Squibb Wyeth) Inject subcutaneously at insertion of deltoid 1 cc Repeat once after an interval of four to six weeks

4 Every econd or third year and immediately after infliction of a penetrating or contaminated wound recall tetanus immunity in the protected with a booster dose of 0 5 to 1 cc of tetanus toxoid alum precipitated

5 The unprotected who have suffered penetrating or contaminated wounds require passive immunization with heterologous antiserum in addition to injection of tetanus toxoid Passive transfer of preformed antibody is required in the lag period between introduction of antigen and development of a sufficiently high titer of antibody to protect against Clostridia

6 Since passive immunization requires use of heterologous serum precede injection by ophthalmic and intradermal sensitization tests using 1 to 10 dilution of serum (p 555) Those with negative responses may be immunized immediately Those with evidences of hypersensi tivity require desensitization (p 4191) In either instance favor pro phylactic use of antihi tamines For the hyposensitive prescribe daily oral do es of 200 mg of pyribenzamine or benadryl to the hypersensi tive give an intramuscular injection of 5 cc of 1% benadryl followed by oral maintenance doses of antihistamine continued for at least two weeks after the last injection of potential allergen

7 Since the nature of the bacterial contaminants of the wound can not be ascertained at the time of decision provide blanket coverage against Clostridia by choosing for passive immunization tetanus and gas gangrene antitoxins combined U S P (Cutter Lederle Lilly National Drug Parke Davis Pitman Moore Squibb U S Standard Products Co Wyeth) Commercial products are packaged so that a single syringe or vial contains 1500 units of tetanus antitoxin and 2000 units each of Cl perfringens and Cl septicum antitoxins After test ing desensitization where necessary and prophylactic administra tion of antihistamine inject 1 unit of combined antitoxins into the wound area and an additional 2 units intramu cularly into deltoid or buttocks Prepare to repeat deposits daily or every second day for at least a week even if superficial appearances are satisfactory

8 In addition to serum prophylaxis deposit 300 000 to 600 000 units of crystalline procaine penicillin G in aqueous suspension for anti biotic protection

9 Finally under local or general anesthesia open the wound to its depth Thoroughly cleanse and irrigate with an oxidizing agent such as 1 4000 potassium permanganate or zinc peroxide (Fig 1159 p 3965 and p 3968)

Immediate Care

1 If possible arrange for hospitalization Inaugurate non specific measures for treatment of the infected patient (p 67) Caution attendants of dangers associated with handling of wound and dressings

2 Send for an endotracheal tube an aspiration suction apparatus and an oxygen tank and mask for emergency u e If unfamiliar with endotracheal intubation summon the specialist anesthetist or laryngologist

3 Discuss advisability of prophylactic rather than emergency tracheotomy (p 3958) Consider well the conclusion of Godman and Adriani (J A M A 141 756 1949) that elective tracheotomy is indicated in all cases of tetanus except the mildest form in which the diagnosis is actually questionable

4 For immediate control of muscle irritability and convulsions for surgical care of the wound and for general anesthesia in the event that elective tracheotomy has been agreed upon choose between tribromoethanol (avertin) administered by rectum and thiopental sodium (pentothal) injected intravenously

5 Unless well staffed elect rectal administration of tribromoethanol (avertin) Prepare 2 5% solution according to directions supplied by manufacturer (p 3837) Approximate a dose of 50 mg of undiluted drug per kilogram of body weight (1 cc per pound of body weight of the 2 5% solution) Instill tested and warmed solution into rectum using male catheter and funnel Hold buttocks firmly together during introduction to prevent expulsion particularly by infants and young children

6 As soon as patient is anesthetized consider elective tracheotomy as previously mentioned incise cleanse and irrigate wound and set up an intravenous drip

7 Into intravenous infusion introduce a priming dose of penicillin Preferably give 10 to 25 million units of crystalline potassium penicillin G dissolved in 100 to 200 cc of physiologic saline solution

8 During course of penicillin infusion make ophthalmic and intracutaneous tests for hypersensitivity to horse serum using diluted material supplied by manufacturer

9 After sensitivity tests have been read and following completion of penicillin infusion introduce 5 cc of 1% benadryl into drip for prevention of hypersensitivity reactions whether or not the patient gives evidences or a history of hyperallergy

10 Desensitize the hypersensitive patient according to technic elsewhere outlined (p 4191)

11 To the hyposensitive individual give massive doses of combined tetanus and gangrene antitoxin If the intravenous drip is still running introduce 100 000 to 200 000 units of antitoxin in 200 to 500 cc of physiologic saline Start the intravenous drip at an initial rate of 30 drops to the minute Increase later to 60 drops per minute if there is no untoward react on Additionally inject into the vicinity of the wound at least 1 unit of combined tetanus and gangrene antitoxins

12 Whether or not the patient is normally or abnormally sensitive

and whether or not antihistamine has been introduced prepare separate barrels containing 1 1000 epinephrine hydrochloride for subcutaneous or intramuscular injection and 1 10 000 solution for direct intravenous introduction in the event that hypersensitivity phenomena are encountered (p 4187)

Continuing Care (Favorable Course)

1 On recovery from general anesthesia even if all appears well continue the intravenous drip for a period of at least twenty four and preferably forty eight hours

2 Maintain antibiotic levels by introduction at 4 to 6 hour intervals of 2 to 5 million units of crystalline potassium penicillin G dissolved in saline solution

3 Continue maintenance of high antibody titers with intravenous introduction of 50 000 to 100 000 units of antitoxin preceded by 5 cc of 1% benadryl for continued antihistamine prophylaxis

4 Irrigate wound frequently with 1 4000 potassium permanganate or with zinc peroxide

5 For general anesthetic effects of tribromo-ethanol or pentothal substitute the combination of phenobarbital with mephenesin (tolserol) Endeavor to keep the patient relaxed but not unconscious Depending on the age of the patient and the severity of symptoms prescribe 0 03 to 0 13 gm (½ to 2 gr) of phenobarbital with 0 062 to 0 750 gm (1 to 12 grains) of mephenesin (marketed as tablets of tolserol each containing 250 mg) Repeat the combined products when restlessness or spasm again reappears In the experiences of Godman and Adriani phenobarbital and tolserol were exceedingly satisfactory in controlling muscular rigidity and spasm in moderately severe tetanus They required repetition on an average of four hours These authors found barbiturates alone given orally rectally intramuscularly or intravenously ineffective in controlling muscular rigidity and spasm of even moderately severe tetanus despite their excellent sedative action Similarly mephenesin without phenobarbital was less effective as a neuromuscular relaxant and unsatisfactory for purely sedative effect

6 As substitutes for phenobarbital mephenesin the practitioner has choice of intravenous procaine curare chloral hydrate and paraldehyde In their study reflecting favorable results with the phenobarbital myanesin combination Godman and Adriani took occasion to test infusions of 0 1% procaine hydrochloride given intravenously in 5% dextrose and d tubocurarine chloride in peanut oil with myricin

7 Of procaine Godman and Adriani state the following

> Procaine used alone is not effective Its stimulating effect on the central nervous system must be overcome with a depressant of the central nervous system (pentothal) In the light of difficulties encountered by experienced anesthesiologists the practitioner treating an occasional patient with tetanus will certainly seek less demanding and less hazardous means for sedation than that offered by intravenous procaine

8 From their experiences with curare Godman and Adriani con

cluded that the results were not always predictable and that treat ment by this method had many of the disadvantages of curare therapy by the multiple dose method as well as the disadvantages of causing massive overdosage

9 Experience with chloral hydrate also resulted in discouraging findings in the hands of these same investigators who concluded that very severe respiratory depression accompanies the doses of chloral hydrate used in all patients

10 Paraldehyde untested by Godman and Adriani is highly regarded by Costello (J Miss M A 46 582) who obtained favorable relaxation with doses of 20 to 40 cc given orally or rectally If tribromo ethanol (avertin) is not readily available paraldehyde may be sub stituted provided that its unpleasant characteristics can be overlooked

Continuing Care (Unfavorable Course)

1 If the problem is essentially that of respiratory failure perform tracheotomy under local anesthesia if the procedure has not already been accomplished Oxygenate preferably in a tent Provide for arti ficial respiration if required

2 If respirations are not seriously depressed and the problem is essentially that of neuromuscular irritability induce general anesthesia preferably with tribromo ethanol (avertin) as previously described Under anesthesia perform tracheotomy and establish intravenous drip

3 Maintain antibiotic levels with introduction of 1 to 25 million units of crystalline potassium penicillin G in saline solution at a rate of 30–60 drops per minute

4 After penicillin infusion has been completed introduce 5 cc of 1% benadryl Follow by 50 000 to 100 000 units of tetanus and gas gangrene antitoxins combined diluted to 200 cc with saline solution

5 Alternate penicillin antihistamine and antitoxin

6 Repeat rectal instillations of tribromo ethanol (avertin) as often as needed the average interval being 3 or 4 hours in severe tetanus (Godman and Adriani loc cit)

7 If neuromuscular irritability persists despite anesthesia pass a stomach tube and introduce an improvised solution made by dis olv ing 4 to 6 tablets each of 250 mg strength of mephenesin (tolserol)

8 Consider intrathecal or intracisternal introduction of antitoxin and antibiotic Opposed by most authorities for reasons elsewhere detailed (p 4409) these procedures are favored by Firor who advises instillations of 15 000 to 20 000 units of tetanus antitoxin under general *anesthesia to which may be added* 25 000 to 50 000 units of penicillin (Bull Johns Hopkins Hospital 62 91)

9 Remember that the effects of tetanus toxin on nerve ti sue do not persist beyond a few days If patient can be sustained over these critical hours recovery may be confidently anticipated Maintain arti ficial respiration and oxygenation as long as heart sounds are audible

10 During the concentration on more imperative problems do not forget less urgent requirements such as catheterization of the urinary bladder and evacuation of the lower bowel

TETRACHLORETHYLENE N F

Tetrachlorethylene ıs a colorle s fluıd used as an anthelmıntıc ın uncınarıasıs (p 1903) ınte.tınal dıstomıasıs (p 1898) ascarıasıs (p 1906) and trıchıurıasıs (p 1906) It ıs the preparatıon of electıon ın uncınarıasıs and ıntestınal dıstomıa ıs but ıs second choıce to hexyl resorcınol (p 4356) ın ascarıasıs and trıchıurıasıs It ıs preferred to carbon tetrachlorıde (p 4198) whıch ıt has replaced because of le ser toxıcıty

Avaılable Products

Tetrachlorethylene N F (ın oft gelatın capsules) 1 cc
CAUTION Dıscard capsules expo.ed to aır (p 1895)

Therapeutıcs

One week precedıng drug Full dıet Avoıdance of alcohol and fat.

Precedıng nıght Salıne purge

Treatment Gıve 3 capsules (3 cc) on arısıng Two hours later Repeat salıne purge Permıt no food untıl bowels have moved Repeat ın three weeks ıf neces ary

Toxıcology

Nausea vertıgo headache (p 1895)

THALAMYD

[Phthalylsulfacetımıde]

A sulfonamıde preparatıon mıdway between oluble and ınsoluble products Unlıke other sulfonamıdes the compound ıs ab orbed ın sub tantıal amounts by the wall of the gut Hence ıt produces ıts effects on the alkalıne ıntestınal tract wıthout causıng detectable sulfonamıde levels ın the blood stream

Avaılable Products

Thalamyd Tablets 0 5 gm (Scherıng)

Pharmacology

Taken orally ın a daıly dosage range of 4 to 8 gm thalamyd reduces the bacterıal count of the stool ın a manner comparable to that of ın oluble sulfonamıdes Partıcularly ensıtıve are Shıgellae Strepto coccus faecalıs Proteus vulgarıs Salmonellae colıform bacıllı and Pasteurellae Wıthın forty eıght hours the bacterıal count ıs reduced to one tenth of the orıgınal numbers of organısms by the seventh day of treatment terıle stools may be obtaıned ın the majorıty of subjects

Like the insoluble sulfonamides therapeutic doses of thalamyd do not produce detectable blood levels However in contrast to older preparations thalamyd diffuses into the intestinal wall penetrating mucosa muscularis and even serosa Separate analyses of the three layers of the intestine reveal appreciable concentrations of thalamyd so that the antibiotic is capable of direct attack on susceptible pathogenic organisms within the intestinal wall (p 4548)

Therapeutics

Recommended doses of thalamyd in dysentery and severe fulminating ulcerative colitis are 3 gm three times daily after meals for ten days In the more chronic forms of ulcerative colitis thalamyd administration must be continued in doses of 2 gm daily for a month or so In abdominal surgery the adult of average weight is given 3 gm five times daily for four to five days pre operatively and for the first two postoperative days

Toxicity

Significant toxicity from thalamyd has not as yet been encountered Except for an occasional tendency to produce frequent loose stools no side effects or untoward manifestations have been reported

THROMBO ANGIITIS OBLITERANS

Principles of Diagnosis and Therapy

1 Regard thrombo angiitis obliterans (p 1029) as a chronic tuberculin type hypersensitivity with predominant manifestations in peripheral arteries and veins (Fig 1177 p 4028)

2 Possible sensitizing allergens are tobacco and the Rickettsiae of typhus fever (p 369)

3 Anti infective agents have no place in the treatment of thrombo angiitis obliterans

4 Specific management includes exclusion of tobacco administration of antihistamine (p 4212) and application for cortisone (p 4145) or ACTH

5 Symptomatic management parallels that for peripheral vascular disease of arteriosclerotic etiology (p 997)

THROMBOSIS AND EMBOLIZATION

(Thrombo embolic Disturbances)

General Principles of Diagnosis and Therapy

1 Extravascular coagulation of circulating blood constitutes a major defense mechanism By contrast intravascular thrombosis is a formidable threat alike in the fields of medicine and surgery (p 1123)

2 Intravascular thrombosis may occur within the lumen of arteries and veins and intramurally within cavities of the heart

3 Arterial thrombotic processes compromise the local vascular basin Protracted ischemia inevitably results in tissue inanition and necrosis as exemplified by gangrene of extremities in peripheral vascular disease and by myocardial infarction secondary to coronary occlusion

4 Venous and intramural thromboses less menacing locally impose the greater hazard of distant embolization as exemplified by pulmonary infarction following peripheral phlebothrombosis and by cerebral infarctions secondary to intramural clotting

5 With successful antibiotic treatment of infectious diseases intravascular thrombosis and neoplastic disease currently share the dubious honor of leadership in the causes of death in the United States

6 Irrespective of the location of the intravascular clot fundamental therapeutic problems are essentially alike Hence the present section includes discussions of phlebothrombosis and thrombophlebitis coronary and cerebral thromboses and peripheral vascular occlusions together with complicating infarctions and embolizations

7 Experienced practitioners internists and surgeons recognize local and systemic predispositions to intravascular thrombosis

8 Local predisposing factors include peripheral arterial disease (arteriosclerosis thrombo angiitis obliterans) peripheral venous disturbances especially varicosities interference with local blood supply (constriction or pressure due to garters binders casts splints bandages stirrups abdominal distention the pregnant uterus abdominal tumors etc) surgical procedures involving structures within abdominal and pelvic cavities particularly hysterectomy prostatectomy appendicectomy and cholecystectomy trauma especially crushing injuries circumscribed infections particularly pyoderms and dermatophytoses and exposure to cold

9 Systemic predisposing factors include constitutional tendencies revealed by the family history generalized vascular disease (arteriosclerosis) metabolic disturbances particularly obesity diabetes and hypothyroidism senility co-existence of wasting disease inadequacies of the circulation due to cardiac irregularities and forward or backward failures (pp 920 and 941) prolonged immobilization the presence of thrombophilia (flabby musculature obesity low basal metabolic rate bradycardia subnormal temperature varicosities and rapid coagulation time) excessive use of or sensitization to products of smoking (p 3384) and thrombocytosis particularly following splenectomy (p 1118)

10 The *prophylaxis* of thrombo embolic disturbances involves efforts to eliminate or neutralize local and systemic predisposing factors More concretely the practitioner aims to improve the local circulation remove factors productive of stasis clear up areas of infection avoid trauma effect weight reduction reduce hyperglycemia correct hypothyroidism by administration of thyroid extract improve muscular tonus by early ambulation and corrective exercises eliminate tobacco

limit use of antibiotics and digitalis restore sinus rhythm preferably with quinidine establish a regimen to relieve the chronic passive congestion of backward failure (p 941) and reduce coagulation time by use of anticoagulant drugs (p 4200) The surgeon assists his medical colleague by sharp and precise technical procedures early ambulation avoidance of constricting bandaging and abdominal distention and by postponement of elective procedures until thrombophiles particularly can be gotten into optimum condition for operative procedure

11 Active treatment of intravascular thrombosis whether arterial or venous is mainly dependent on cautious and considered use of anticoagulant drugs For the general practitioner at least the current preparation of choice is heparin deposited subfascially according to the technic of Loewe

12 Supplementary surgical procedures aimed at relief of thromboses or embolizations include induction of sympathetic blockade ligation of thrombosed vessels thrombectomy embolectomy and amputation Each technical procedure requires at least temporary interruption of anti coagulant therapy

13 Experienced physicians who have lived through the treacherous hazards of intravascular thrombosis need not be reminded that there is no such thing as a mild or insignificant phlebothrombosis Each individual attack is a precarious complication which may terminate fatally at any given moment despite what appear to be insignificant local manifestations

TESTS OF COAGULABILITY

Coagulation Time (Lee White Howell)

The bedside method for estimation of coagulation time is technically simple However results will be inaccurate and misleading unless each detail is executed with meticulous accuracy

Equipment

1 2 cc syringe with 18 or 20 g needles 1½ long
2 4 test tubes (75 x 10 mm)
3 Test tube rack

CAUTION Syringes needles and test tubes must be thoroughly cleaned and absolutely dried Whether purchased new or used previously rinse equipment in cold water clean with a brush wash with wetting solution (Alconox Scientific Standards Co New York N Y) rinse again with water and drain until thoroughly dried Before sterilization and assembly test barrel and piston to assure a snug fit since admixture of aspirated air bubbles destroys accuracy of tests Dry sterilize both syringes and needle preferably in autoclave

Technic

1 Clean skin thoroughly with alcohol Wait for complete drying since contamination with alcohol invalidates results

2 Enter vein by precise puncture Fumbling venipunctures produce false readings from contamination with tissue juices If vein is not cleanly negotiated, select another vessel even though this means an additional puncture for the patient.

3 Using only gentlest suction on piston withdraw 2 cc of blood Note precise time

4 Withdraw needle and disconnect from barrel of syringe

5 Gently transfer about one finger breadth of blood into each of 4 test tubes previously placed in a test tube rack Discard blood that has been admixed with air

6 Wait patiently for five minutes protecting tubes from jarring or agitation

7 After five minutes remove first tube from rack and make following observations

(a) Does the blood have a uniform appearance or is there a separation into clear supernatant plasma and sediment of erythrocyte ? Thoroughly heparinized blood clearly separates

(b) On tilting how rapid is flow of blood? Blood that is about to clot flows slowly as a sludge thoroughly heparinized blood flows rapidly

(c) On tilting is surface level of blood quite uniform or is it wavy? Blood that is about to clot appears uneven heparinized blood has a clear linear surface level

(d) Has any blood adhered to inner surface of tube? Blood that is about to clot adheres in patches heparinized blood reveals no evidence of stickiness

(e) Can test tube be inverted without spillage? Clotted blood jells completely whereas fluid heparinized blood spills

(f) Under the same careful conditions described for the first tube make identical visual observations successively on the second third and fourth tubes Do not agitate any tube until its predecessor has thoroughly clotted and can be inverted without spillage

(g) Report the coagulation time as the span between withdrawal of blood from the vein and complete clotting in the fourth tube This eliminates the error that is necessarily introduced by observation and agitation of the first three tubes during the course of preliminary inspections

(h) Under normal conditions the coagulation time varies between eight minute on the low side and fifteen minutes on the high side More rapid clotting is encountered in thrombophiles delayed coagulation is seen in hemophilia and treated patient who are either satisfactorily heparinized or hyper heparinized (failure of coagulation before one hour)

(i) Careful observers will note technical differences in the bedside coagulation texts There may be considerable variation in the respective coagulation times of each of the four tubes On this account experienced clinicians place greater reliance on separation of serum from cells as an index of adequate heparinization So long as the cells settle and leave a clear supernatant fluid the therapeutic goal of rendering the circulating blood relatively uncoagulable has been accomplished

Prothrombin Activity (Quick)

Reagents

1 Commercial preparation of rabbit brain dehydrated with acetone

2 Physiologic saline

3 10th molar sodium oxalate made by dissolving 1 34 gm in 100 cc of sterile distilled water

4 40th molar calcium chlorid solution made by dissolving 0 278 gm. of the anhydrous salt in 100 cc of water

5 Sterilized and thoroughly dried 2 cc syringes and needles prepared as for estimation of coagulation time (p 4572)

6 Centrifuge

7 Water bath

8 Time clock

9 Thromboplastin reagent made by mixing 0 15 gm thromboplastin (Difco) and 2 85 cc of saline in a test tube (9 x 100 mm) placed in a water bath of 45 -50 C for ten minutes mixed and let stand for sedimentation of coarse particles after which 2 cc of the supernatant fluid is removed and stored in a stoppered vial at 5 C

Technic

1 Obtain blood by venipuncture under precautions employed for coagulation time (p 4572)

2 To a graduated centrifuge tube containing 0 2 cc sodium oxalate (M/10) add sufficient blood to bring to 2 0 cc volume Mix thoroughly

3 Into each of three test tubes (9 x 65 mm) introduce 0 1 cc saline 0 1 cc plasma and 0 1 cc thromboplastin Stand at room temperature for fifteen minutes
4 Warm tubes in water bath at 37° C for one minute add to each 0 1 cc calcium chloride (M/40) previously warmed to 37 C
5 Start stop watch at instant of addition of calcium salt
6 Keep tubes in water bath for five seconds
7 Remove tubes and observe against source of light Invert to observe exact time of clot formation and record the number of seconds

Calculation

$$\frac{\text{Prothrombin Time of Control}}{\text{Prothrombin Time of Patient}} \times 100 = \text{per cent prothrombin activity}$$

Link and Shapiro Modification of Quick Method

The Committee of the American Heart Association studying anticoagulant therapy of coronary thrombosis favors estimation of prothrombin activity by the Link Shapiro modification of the Quick method

Reagents [Link Shapiro]

1 Thromboplastin Reagent (Maltine) Add 50 mg of commercial thromboplastin to 2 5 cc of normal saline Keep mixture in water bath at 50 to 55 C for 10 minutes Cool to room temperature Add 2 5 cc of M/40 calcium chloride Stir with glass rod for four minutes Centrifuge for ten minutes
2 Physiologic saline
3 M/10 sodium oxalate (p 4573)
4 M/40 calcium chloride (p 4573)
5 Sterile dry 2 cc syringe and needles as prepared for estimations of coagulation time (p 4572)
6 Centrifuge
7 Water bath
8 Time clock

Technic

1 Obtain at least 5 0 cc of whole blood by clean venipuncture as for estimation of coagulation time (p 4572) Simultaneously or shortly thereafter obtain blood similarly from a normal control
2 Transfer 4 5 cc of each blood specimen to a clean test tube containing 0 5 cc of M/10 sodium oxalate
3 Send specimens immediately to clinical pathologist
4 Centrifuge blood specimen to separate plasma from erythrocyte sediment
5 To 0 2 cc of thromboplastin reagent add 0 1 cc of plasma Place in water bath at 37 5 C
6 With stop watch note time of clot formation in patient s blood and normal control

Calculation

Calculate prothrombin activity according to the formula

$$C = \frac{k}{p\,t - a}$$

C = concentration or prothrombin activity in per cent of normal
p t = prothrombin time
k = constant with value of 303
a = constant with value of 8 7 provided that the reading for normal plasma is 12 seconds

If prothrombin time of the normal exceeds thirteen seconds dilute plasmas with one four and eight parts of isotonic sodium chloride solution Repeat tests and report in terms of 50% 20% and 12 5% activity

Alternate Technic [Ziffren Owen Hoffman and Smith]

1 Using Niphanoid (Winthrop) make fresh thromboplastin solution according to manufacturer s directions
2 Place 0 1 cc of thromboplastin reagent in each of several small test tubes
3 Make venipuncture as described (p 4572) Mix 0 9 cc of whole blood with thromboplastin
4 Simultaneously obtain blood from normal control Carry out test in duplicate
5 Gently tilt each tube until clot is formed Note time
6 Compare clotting time of normal with clotting time of patient

$$\frac{\text{Clotting Time of Normal}}{\text{Clotting Time of Patient}} \times 100 = \text{per cent prothrombin activity}$$

Criticisms and Difficulties in Estimations of Prothrombin Activity

(a) The test requires venipuncture of a healthy individual each time the patient s blood is examined If the normal control exceeds thirteen seconds the report must be withheld
(b) A fresh preparation of prothrombin must be made up daily The technic of pro cedure is exacting and for a full time technician rather than for the practicing physician
(c) Methods of calculating prothrombin activity in the various tests vary and do not corre pond Some workers report in per cent of normal while others report time in seconds There is no correlation between the two sets of figures The American Medical Association gives its approval to the expression of prothrombin activity in per cent of normal Yet D C Rivers concludes that it might be wise to discard percentage reports entirely and to report in seconds with the normal also given in seconds
(d) Finally the formulas used to calculate the per cent of normal vary and do not correspond The method in general use according to directions of manufacturers of thromboplastin and authoritative texts of clinical pathologists employ the simple arith metical calculation of dividing the normal (expressed in seconds) by the unknown (expressed in seconds) The answer is mult plied by 100 to give per cent of normal according to the formula

$$\frac{\text{Normal}}{\text{Unknown}} \times 100 = \% \text{ of normal}$$

The American Medical Association favors the formula

$$C = \frac{k}{pt - a}$$

In the above equation C is the concentration of prothrombin activity expressed as per cent of normal p t is the prothrombin time k and a are constants which have respective values of 303 and 8 7 provided that 12 seconds is the reading for the normal control It is the opinion of the respondent in Queries and Minor Notes that calculation of the prothrombin per cent by dividing the normal by the abnormal is entirely erroneous

PHLEBOTHROMBOSIS (THROMBOPHLEBITIS)

Practical Management

Prophylaxis

1 Reduction of morbidity and mortality through introduction of effective antibiotics in the treatment of infectious diseases leave phlebothrombosis and thrombophlebitis as major complications causing incapacitation and death in medical and surgical practice
2 In protracted and chronic illnesses and in postoperative periods consider the potential complication of phlebothrombosis in each patient who presents local or systemic predisposition to intravascular clotting (p 4571)

3 During the course of each protracted or chronic illness and following pregnancy and surgical procedures known to predispose to intravascular clotting guard against phlebothrombosis the more particularly if it is known that the patient additionally exhibits contributing tendencies to thrombosis

4 To lessen patient predisposition to intravascular clotting insist on weight reduction by dietary means (p 669) control of hyperglycemia and glycosuria (p 1252) correction of hypothyroidism through administration of thyroid extract (p 1190) abstinence from use of tobacco (p 3884) accomplishment and maintenance of good muscular tonus through exercise (p 3756) restoration of sinus rhythm in cardiac irregularities particularly through use of quinidine (p 873) and prevention or relief of stasis due to backward failure (p 945)

5 To minimize postoperative phlebothrombosis particularly in the thrombophile postpone elective surgery until the previously described constitutional predispositions have been minimized insist on precise and gentle surgery in the hands of the most expert technician urge careful hemostasis avoid use of stirrups especially during pregnancy gynecologic and urologic procedures prevent abdominal distention by gastric intubation forbid use of tight abdominal binders circular splints and casts and of measures which limit free chest expansion request application of elastic bandages to extremities before removal from operating room on return to bed assume head down position to favor return of venous blood from lower extremities instruct nurse to urge deep breathing exercises as soon as consciousness is recovered order ventroflexion of toes against resistance many times daily and advocate early ambulation (p 4122)

6 During protracted medical illnesses and in postoperative periods particularly under circumstances which predispose to intravascular clotting consider use of anticoagulants As soon as hemostasis is secure deposit heparin subfascially (p 4203) Use somewhat smaller doses than employed for treatment of overt phlebothrombosis approximating 200 mg for lighter patients and 250–300 mg for those who weigh more than 150 lbs Prophylactic anticoagulant therapy following abdominal hysterectomy at the Mayo Clinic effected a reduction in phlebothrombosis in the ratio of 11 to 1 of pulmonary embolism from 50 to 1 and of fatal thromboembolic disease from 86 to 1

7 Continue daily deposits of heparin as indicated by bedside estimations of coagulation time (p 4572) until patient is completely ambulant and well on in convalescence

Immediate Care

1 Consider complication of phlebothrombosis in each patient who presents local or systemic predispositions to intravascular clotting the more particularly if exposed to protracted illness or surgical procedures known to contribute to the phenomenon of intravascular clotting (p 4571)

2 Do not delay diagnosis of intravascular thrombosis until classical signs of thrombophlebitis make their appearance There may be exten

sive intravascular clotting long before patient complains of local pain and tenderness and considerably prior to notation of palpably indurated vessels or pain on ventroflexion of the extended leg (Homan's sign)

3 The early signs of phlebothrombosis are insidious Suspect intravascular thrombosis when without other overt causation convalescence appears not to be as rapid as might be expected temperature fails to reach basal pre-operative level even though elevation does not exceed 0 5 to 1 F and never rises above 100 F when there is an otherwise inexplicable relative tachycardia as compared to basal rate per minute when there is a slight increase in the respiratory rate when the patient just does not look right and when there are transitory and relatively negligible complaints of occasional dizziness chest pain or limitation of inspiration by a sudden catch for contrary to general belief earliest signs of phlebothrombosis may be those of complicating embolization

4 Do not wait until physical signs are apparent in legs or chest to diagnose phlebothrombosis or pulmonary embolizations There may be multiple infarcts of moderate size before there are audible manifestations of hazardous complications

5 Do not wait until there are roentgen signs of pulmonary embolization Chest radiographs are notoriously misleading they may be unrevealing when subjective manifestations are definitive and when localized physical signs are picked up by the inquiring ear

6 Do not delude yourself by the belief that there is any such thing as a mild or unimportant phlebothrombosis Each attack is a potentially precarious and hazardous complication which may terminate fatally Do not lull yourself into a sense of security by enunciation of the hopeful prognosis which necessarily must be given to the patient

7 Whether the diagnosis of phlebothrombosis is definitive or only suggestive immediately immobilize the patient completely

8 Get rid of all possible factors predisposing to venous stasis remove abdominal bandages and circular splints or casts reduce abdominal distention through gastric intubation or a gentle rectal flush forbid smoking discontinue digitalis and antibiotics unless indications for use of these products are urgent

9 Determine blood coagulation time by the bedside method of Lee White and Howell (p 4572)

10 If there is pain or edema of involved phlebitic area perform sympathetic block of lumbar ganglions (p 4579)

11 Deposit heparin subfascially with or without vasoconstrictor Estimate dose according to patient's weight and length of coagulation time (p 4203) Unless contraindicated by hypertension prefer product with vasoconstrictor

12 Precede deposit of anticoagulant with subcutaneous injection of an analgesic preferably demerol 100 mg or dolophine 2 5 to 5 mg Warn patient of possibility of pain within a few hours after deposition of anticoagulant Leave orders for repeat doses of analgesic as required

13 Unless apprehension or expense are deterrents favor oxygen

3 During the course of each protracted or chronic illness and following pregnancy and surgical procedures known to predispose to intravascular clotting guard against phlebothrombosis the more particularly if it is known that the patient additionally exhibits contributing tendencies to thrombosis

4 To lessen patient predisposition to intravascular clotting insist on weight reduction by dietary means (p 669) control of hyperglycemia and glycosuria (p 1252) correction of hypothyroidism through administration of thyroid extract (p 1190) abstinence from use of tobacco (p 3884) accomplishment and maintenance of good muscular tonus through exercise (p 3756) restoration of sinus rhythm in cardiac irregularities particularly through use of quinidine (p 873) and prevention or relief of stasis due to backward failure (p 945)

5 To minimize postoperative phlebothrombosis particularly in the thrombophile postpone elective surgery until the previously described constitutional predispositions have been minimized insist on precise and gentle surgery in the hands of the most expert technician urge careful hemostasis avoid use of stirrups especially during pregnancy gynecologic and urologic procedures prevent abdominal distention by gastric intubation forbid use of tight abdominal binders circular splints and casts and of measures which limit free chest expansion request application of elastic bandages to extremities before removal from operating room on return to bed assume head down position to favor return of venous blood from lower extremities instruct nurse to urge deep breathing exercises as soon as consciousness is recovered order ventroflexion of toes against resistance many times daily and advocate early ambulation (p 4122)

6 During protracted medical illnesses and in postoperative periods particularly under circumstances which predispose to intravascular clotting consider use of anticoagulants As soon as hemostasis is secure deposit heparin subfascially (p 4203) Use somewhat smaller doses than employed for treatment of overt phlebothrombosis approximating 200 mg for lighter patients and 250–300 mg for those who weigh more than 150 lbs Prophylactic anticoagulant therapy following abdominal hysterectomy at the Mayo Clinic effected a reduction in phlebothrombosis in the ratio of 11 to 1 of pulmonary embolism from 50 to 1 and of fatal thromboembolic disease from 86 to 1

7 Continue daily deposits of heparin as indicated by bedside estimations of coagulation time (p 4572) until patient is completely ambulant and well on in convalescence

Immediate Care

1 Consider complication of phlebothrombosis in each patient who presents local or systemic predispositions to intravascular clotting the more particularly if exposed to protracted illness or surgical procedures known to contribute to the phenomenon of intravascular clotting (p 4571)

2 Do not delay diagnosis of intravascular thrombosis until classical signs of thrombophlebitis make their appearance There may be exten

Continuing Care (Unfavorable Course)

1 With increasing phlebothrombosis extension involvement of new vessels or embolization ask for consultation with a surgeon for dis cussion of operative intervention

2 If surgical procedure is advised discontinue heparin and nullify its anticoagulant effect by intravenous introduction of whole blood or of 2% protamine (p 4204)

3 If vessel ligation is to be done insist on bilateral ligations of femoral veins and all branches Remember that phlebothrombosis is rarely if ever a limited pathologic process and that more than half of the patients reveal extension above Poupart s ligament

4 At operation favor manual or suction removal of clot from above central ligated segment In pelvic proces es (as seen following preg nancy hysterectomy prostatectomy and appendicectomy) discuss ligation of inferior vena cava

5 Following operation resume procedures indicated under Imme diate Care (p 4576)

6 In convalescence insist on adherence to prophylactic regimen in order to prevent recurrence

SURGERY OF THROMBO EMBOLIC DISTURBANCES

Surgical procedures of supplementary value in the treatment of thrombo embolic disease include lumbar sympathetic blocks for processes involving the lower extremities stellate sympathetic block for thromboses of the cerebrum or upper extremities venous ligations or interruptions where the thrombotic proce s appears sharply localized thrombectomy and embolectomy

Lumbar Sympathetic Block

Many ymptoms and signs of thrombophlebitis are due to vasospasm of arterial and venous sy tems secondary to vasoconstricting impulses originating in the thrombophlebitic segment As the result of vaso pasm there result increased filtration pressure relative anoxia of the capillary endothelium and diminution in the flow of lymph all of which increase the amount of perivascular fluid as manifested clinic ally by edema By interruption of vasoconstrictor impul es with pro caine hydrochloride infiltration of sympathetic ganglions re establish ment of the normal exchange of intravascular and perivascular fluids is accomplished

The technic of lumbar sympathetic block is within the technical range of any physician capable of performing lumbar puncture Suc cessfully accomplished procaine block promptly relieves pain reduces fever and results in dissipation of edema within a few days Required technical steps are as follows

(a) If anticoagulant drug has not yet been administered withhold for a few hours after the technical procedure has been accom plished

therapy preferably in a tent whether or not there are menacing systemic symptoms such as cyanosis, air hunger tachypnea tachy cardia pallor diaphoresis and other evidences of forward failure (p 920) *Free oxygenation may be depended on to diminish sludge* formation and to lessen tissue damage in infarcted areas

14 During critical first few hours and days give little heed to fluid and food requirements Permit patient to drink and swallow soft foods according to whim

15 If analgesics do not provide sufficient sedation and hypnosis additionally order oral barbiturates Prescribe 30 mg of phenobarbital every three or four hours during the day and 90 to 180 mg of sodium seconal or any one of its substitutes at bedtime together with a warm drink

16 For protection of patient and your own reputation maintain a constant vigil as unobstrusively as possible Try to prevent other visits to the patient Do not be overzealous in physical examinations Limit surveys to what can be learned without turning the patient or sitting him up

17 Unless especially trained and equipped with unusual facilities avoid use of Dicumarol as an anticoagulant (p 4203)

Continuing Care (Favorable Course)

1 Make daily estimates of blood coagulation time (p 4572)

2 Depending on bedside test decide upon deposits of heparin Try *to keep coagulation time between twenty and thirty minutes* by use of 200 to 400 mg of heparin with or without vasoconstrictor deposited at 24 36 or 48 hour intervals as indicated

3 So long as patient is comfortable and contented maintain oxy gen therapy

4 When necessary empty lower bowel by a simple rectal flush Do not permit patient to strain on bed pan

5 At end of week resume normal diet if all is well

6 After ten days to two weeks begin leg exercises by contraction of quadriceps and ventriflexion of feet against resistance

7 Have patient measured for elastic stockings to extend from toes to mid thighs so that they may be ready when ambulation is resumed

8 Sometime in the second or third week depending on circum *stances, apply elastic bandages and permit dangling for* five to ten minutes twice daily

9 Increase activity to weight bearing permitting patient to stand on feet long enough to get out of bed and sit in a chair

10 Permit daily trip to lavatory for evacuation

11 Increa e range of activity until patient has the privilege of walk ing around the room and then through corridors or rest of house

12 After three weeks if all is well reduce numbers of heparin injec tions to twice weekly Continue maintenance doses for another two or three weeks as indicated

13 Warn patient of possible recurrence Institute prophylactic pro cedures previously described (p 4575)

Vessel Ligation

If intravascular thrombosis were a purely localized process surgical therapy by ligation or interruption of the involved vessel would rapidly provide satisfactory surgical control Unfortunately for an easy solution to a hazardous problem intravascular thrombosis is rarely an isolated pathologic lesion To be sure the leg vessels and most particularly those of the calf are involved in the vast majority of phlebothrombotic disturbances Nevertheless extensive studies reveal that thrombotic occlusion extends above the level of Poupart s ligament in more than 50% of instances and as a result surgeons have successively recommended local excision saphenous ligation unilateral femoral ligation bilateral femoral ligation and finally ligation of the inferior vena cava

Greater assurance with heparin anticoagulant therapy and misgivings concerning surgical procedures in patients who are often desperate risks have diminished enthusiasm for operative interference in most quarters We are included in the lists of those who currently oppose surgical interference for intravascular thrombosis except where indications are unusual (sharply localized vessel involvement failure of anticoagulant therapy and/or repeated embolic phenomena)

Thrombectomy

Removal of intravascular thrombi central to the ligated or excised vessel (by forceps or by catheter suction) is a hazardous but necessary accompaniment of operative procedures involving thrombosed veins

Embolectomy

Projection of the intravascular thrombus through the cardiac chambers and into lungs or cerebrum constitutes a dramatic emergency of clinical practice In completely equipped institutions teams organized for immediate removal of occluding thrombi function to save life at best or embolized tissue at the least Ina much as the procedure must be carried out within a very few minutes of the accident the scope of the problem is far beyond the capacities of the general practitioner who should none the less have access to experts equipped for these potentially life saving procedures

THROMBOSIS CEREBRAL

Practical Management

Prophylaxis

1 Observe prophylactic precautions pertinent to coronary thrombosis (p 4583)

(b) If anticoagulant drug is still effective inject antidotal protamine if heparin has been employed
(c) Place patient in lateral recumbent position as for lumbar puncture (p 3782)
(d) Mark upper levels of spinal processes of first four lumbar vertebrae
(e) Mark points 2½ finger breadths lateral to and horizontal with upper levels of these spinal processes The respective transverse processes of these four lumbar vertebrae lie immediately beneath the lateral points
(f) Insert lumbar puncture needles vertically through each lateral point previously marked When needle is felt to impinge on the transverse process change direction slightly so that tip is directed beneath the transverse process and mesially to approach anterolateral surface of body of vertebra where the sympathetic chain lies
(g) When position of the needle has been changed carefully and slowly insert an additional 2½ finger breadths
(h) Aspirate frequently to ascertain that needle tip is not within lumen of any vascular structure
(i) Slowly inject 5 cc of 1% procaine
(j) Repeat procaine injections in each of other four lumbar sympathetic ganglia
(k) Repeat after twenty four to forty eight hours if necessary

Stellate Ganglion Block

1 Place pillow under shoulders of the supine patient and turn head to side opposite from site of proposed injection

2 Palpate transverse processes of lower cervical vertebrae

3 Place skin wheal over sixth transverse process palpable even in patients with thick short necks This point is approximately one finger breadth superior to sternoclavicular articulation

4 With free hand displace the sternocleidomastoid muscle slightly mesially to preclude piercing with needle

5 Insert a 22-gauge 4 inch needle through skin wheal in line with sternoclavicular articulation

6 Direct needle posteriorly toward plane through spine of seventh cervical vertebra until bone contact is made

7 Withdraw needle 1 mm Aspirate to ascertain that lumen of vessel has not inadvertently been entered

8 Slowly inject 2 cc of 1 to 2% procaine hydrochloride aspirating repeatedly during procedure to preclude possibility of false entry into vessel spinal canal or pulmonary tissue

9 Look for evidences of Horner s syndrome (ipsolateral ptosis and pupillary miosis) If the syndrome does not develop within a few moments inject another 3 cc If still unsuccessful conclude that the ganglion has not been injected and preferably seek assistance of consulting anesthesiologist

50% glucose or sucrose (Sorbitol) in amounts varying from 20 to 100 cc

10 Venesection once widely utilized is of no value unless to combat polycythemia or congestive heart failure

11 Rehabilitation of the hemiplegic requires the urgent attention of the practitioner Begin active therapy as soon as patient regains con sciousness In the early stages of treatment start the following procedures to prevent deformity

(a) Arrange foot board or posterior leg plint to prevent foot drop

(b) Use sandbags to combat outward rotation of affected leg

(c) Place pillow in axilla to counteract adduction of shoulder

(d) Institute quadriceps exercises to maintain muscle strength

12 Attach a pulley to a gooseneck pipe over head of bed using an ordinary clothesline rope with a 1 inch webbing for the hand loop Teach stretching and passive pulley exercises to increase range of motion of shoulder and elbow and prevent adhesions

13 Start speech therapy as soon as pulley exercises have gotten under way

14 Inaugurate retraining in ambulation Start by practice of balance in the standing position and progress to parallel bars Teach heel and toe gait stressing reciprocal motion to minimize clonus and reestablish normal walking habits Use a short leg brace to correct foot drop If parallel bars are not available substitute two kitchen chairs

15 Teach crutch walking starting with alternate 4 point gait and stressing climbing of steps curbs stairs and ramps Concurrently retrain in activities of self care and daily living such as use of knife and fork buttoning clothes etc

THROMBOSIS, CORONARY

[Coronary Occlusion]

Practical Management

Prophylaxis

1 Currently coronary thrombosis is a major cause for incapacita tion and death in middle and old age groups Increasingly coronary thrombosis is recognized as a cause for sudden exodus in young men as revealed by an incidence of 300 in a group of 800 non accidental non combat deaths in apparently healthy oldiers

2 As in the case of phlebothrombosis there exist constitutional and acquired predispositions to the process of intravascular clotting

3 In his routine survey of the office population the sea oned prac titioner devises methods of preventing or delaying coronary thrombosis in likely candidates particularly males

4 More specifically he advises weight reduction (p 669) correc tion of hypothyroidism by administration of thyroid extract (p 1189)

Immediate Care

1 Cerebral thrombosis more frequently encountered than cerebral hemorrhage is characterized by its ingravescent onset Small and even larger thrombi in silent areas most often produce transitory and seemingly minor clinical manifestations in contradistinction to the classical stroke or shock The small signs of ingravescent cerebral thrombosis include amnesia aphasia, muscle weakness vertigo disequilibration ataxia, awkwardness slow cerebration stumbling somnolence or restlessness alone or in combination and of transitory or longer duration

2 The seasoned practitioner who lives his life with his patient recognizes these changes though there are no demonstrable deviations in the neurologic physical examination

3 Satisfied that the patient is suffering an ingravescent cerebral thrombosis deposits of heparin as previously described are warranted (p 4203)

4 In general the patient is then cared for in the manner of those who suffer coronary thrombosis except that oxygen therapy is not so urgently required

5 In the event that the patient suffers the characteristic hemiplegia blockade of stellate ganglion with procaine is distinctly indicated in the manner of lumbar block in phlebothrombosis

6 To practice stellate ganglion injection place patient supine with pillow beneath the shoulders and head turned to side opposite from site of injection Palpate transverse processes of lower cervical vertebrae Place skin wheal over sixth transverse process which corresponds approximately to a spot 2 cm (one finger breadth) above sternoclavicular articulation With free hand displace sternocleidomastoid muscle slightly medially to preclude piercing with needle Using a 4 inch (10 cm) 22 gauge needle penetrate wheal until contact is made with tip of transverse process Then guide needle tip along anterosuperior surface of transverse process until it reaches body of vertebra Slightly withdraw needle and aspirate to be sure that neither vessel lumen spinal canal nor air containing pulmonary tissues have been pierced Slowly inject 2 cc of 1 to 2% procaine With needle in situ wait five to ten minutes looking for evidences of Horner s syndrome (ipsolateral ptosis and pupillary miosis) If these signs fail to appear inject an additional 3 to 5 cc slightly moving tip of needle

7 If stellate ganglion injection is unsuccessful by method above described summon consultant anesthesiologist

8 Because of the semi conscious or comatose condition of the patient who has had a cerebral accident it is necessary to protect with anti infective agents For this purpose despite its tendency to favor increased coagulability of blood deposit 300 000 to 600 000 units of procaine penicillin G in aqueous suspension or oil repeating after twelve to twenty four hours if necessary

9 Intravenous injection of hypertonic solutions for reduction of intracranial pressure is worthy of consideration For this purpose use

13 Particularly avoid digitalization unless there are definitive evidences of backward failure

14 Avoid antibiotics especially penicillin and aureomycin unless there are definitive evidences of superimpo ed infection Each of these antibiotics tends to increase blood coagulability

15 Avoid sudden changes in blood pressure induced by overzealous injection of adrenergens Rely on vasoconstrictor incorporated in heparin product for more sustained effects

16 Unless especially trained and equipped with unusual facilities avoid use of Dicumarol as an anticoagulant (p 4202)

Continuing Care (Favorable Course)

1 Continue oxygen therapy for at least a week or ten days even if all is well

2 Sedate during day with phenobarbital 15 to 30 mg (¼–½ gr) every three or four hours as needed

3 Prescribe a hypnotic such as sodium seconal 90 mg (1½ gr) on retiring Repeat if neces ary

4 With continued or recurrent pain inject subcutaneously 100 mg of demerol or 5 mg of dolophine Re erve intravenous injection of 2 mg (1/32 gr) of dilaudid for sustained or severe discomfort

5 Take bedside coagulation time each day Deposit heparin as needed (p 4203) Precede heparin injection with subcutaneous demerol or dolophine if patient is apprehen ive or suffers during introduction of anticoagulant Leave orders for repetition of analgesic if heparin reaction occurs after deposit

6 Make no attempt to maintain fluid or food intake Unless patient is thirsty or hungry permit almost complete hibernation If patient requests food or drink give whatever is requested within reason but avoid iced or carbonated drinks or fruit juices which may produce distention

7 Unless patient is distended or uncomfortable ignore constipation If there is discomfort turn on left side and have an experienced nurse give a low rectal flush or irrigation

8 Repeat electrocardiographic trace once or twice weekly

9 Do not be disturbed by transitory temperature elevations which may be aseptic as the result of infarction itself or of introduction of heparin

10 After ten days to three weeks depending on estimated extent of myocardial infarction and patient s response to therapy consider initiation of convalescence Encourage ventriflexion of feet and contraction of quadriceps to maintain muscle tone and prevent phlebothrombosis Continuing heparinization bandage legs and permit dangling at side of bed

11 If minor activity is favorably received permit weight bearing so that patient may sit at side of bed Later suggest a trip to lavatory for purposes of evacuation

12 After three to six weeks if all is well reduce heparin injections

control of diabetes mellitus (p 1252) reduction or preferably elimination of use of tobacco (p 3884) maintenance of good muscular tone by non competitive exercise (p 3756) maintenance of a normal blood pressure (p 4360) and *lessening of tensions and strains of every-day existence* (p 3473)

5 By insistence on routine annual electrocardiographic tracings and teleo roentgenograms after age of 35 the diagnosis of closure of *small coronary twigs is greatly facilitated* permitting intensive therapy when seemingly minor deviations are reported

Immediate Care

1 *Do not await classical clinical manifestations of coronary thrombosis* before making diagnosis and instituting therapy (p 983) Obtain serial electrocardiograms for comparison with office records whenever patient complains of even minor degrees of precordial oppression or pain discomfort radiating up toward neck or down arms and otherwise *inexplicable evidences of forward failure particularly faintness* dizziness an all-gone feeling profuse perspiration etc

2 Do not lightly dismiss attacks as mere coronary insufficiencies (p 895) *Remember that coronary insufficiency also is a manifestation* of organic coronary closure (EKG 6–14 pp 814–818)

3 Even on suspicion of diagnosis immobilize completely at home if facilities are adequate Preferably avoid hospitalization which requires transportation and strain and involves additional expense

4 Inject intravenously 2 mg (1/32 gr) of dilaudid if pain and distress are great Otherwise give subcutaneously 100 mg of demerol or 5 mg of dolophine

5 Insist on oxygen therapy even in mildest occlusions *Use a mask* if necessary but preferably obtain a tent

6 Limit examinations to cardiac auscultation notation of blood pressure electrocardiographic trace and estimation of blood coagulation time by *Lee White Howell bedside method* (p 4572)

7 On basis of estimated weight and calculated coagulation time deposit heparin even in seemingly mild occlusions (p 4203) Inject subfascially 200 to 300 mg in lighter patients and 300 to 400 mg in those who weigh more than 150 lbs *Unless patient is hypertensive* give at least half the dose with vasoconstrictor (p 4203)

8 Caution patient of possible local reaction to heparin Leave orders for repetition of analgesic as needed

9 *Despite therapeutic reassurance* to the patient do not delude yourself that there is any such thing as a minor coronary thrombosis

10 Maintain a constant vigil unobstrusively and demand professional nursing care if possible

11 Ignore fluid and food requirements Once patient has been sedated heparin has been deposited and oxygen therapy instituted practice skillful neglect

12 In the presence of *any cardiac irregularity consider* oral administration of 0 3 gm (5 gr) of quinidine sulfate every three or four hours until sinus rhythm has been restored for at least two or three days

Therapeutics

In uncinariasis (p 1903) after failure of tetrachlorethylene and hexylre orcinol thymol may be tried with caution The evening pre ceding treatment a saline purge is given On the morning of treat ment 3 capsules (900 mg) are given at hourly intervals for three doses to total 2 7 gm A saline purge is given after the last dose

Treatment may be repeated after a week and if there has been no toxicity the dose may be increased to 4 capsules (1200 mg) repeated three times at hourly intervals to total 3 6 gm

Toxicity

Nausea vomiting diarrhea convulsions respiratory and circulatory depression (p 1897)

TICK BITE FEVER

Principles of Diagnosis and Therapy

1 In addition to acting as vectors in infectious diseases (Table 2 p 42) ticks secrete a toxin which may produce fever and paralysis in the host (p 41)

2 Removal of the tick eliminates symptoms

3 Because of their potential transmission of rickettsial diseases (Rocky Mountain spotted fever) bacterial invasions (tularemia) and spirocheto es (relapsing fever) prophylactic antibiotic therapy merits consideration in the tick infe ted Aureomycin and/or chloramphenicol are specific in rickettsemias and gram negative bacillary infections but penicillin is most effective against Borrelia recurrentis The combina tion of a single depo it of 600 000 units of procaine penicillin G in oil with 2% aluminum monostearate and of 3 gm orally of aureomycin or chloramphenicol daily for three days may be expected to prevent or abort all invasions transmitted by the tick

TORULOSIS

[Cryptococcosis]

Principles of Diagnosis and Therapy

1 Torulosis is a yeast invasion with selective localization in the central nervous system (p 442) and lungs (Fig 79 p 497)

2 The diagnosis is made by demonstrating organisms in cerebro spinal fluid or sputum

3 Successful treatment has been reported with sulfadiazine Other investigators found no inhibition with various sulfonamides as well as streptomycin and penicillin but noted an inhibitory effect with gentian violet

to twice weekly for perhaps another month Permit patient to walk about room and later through house or corridors

13 In convalescence discuss prophylactic measures emphasizing that recurrences of coronary thrombosis are the rule rather than the exception Temper this gloomy prospect by assurance that strict adherence to preventive measures offers high promise for restitution to normal within limits

Continuing Care (Unfavorable Course)

1 With recurrence of thrombosis or evidences of extension make no significant changes in previously outlined regimen Check to be sure that sufficient heparin has been administered to raise coagulation time beyond thirty minutes increase oxygen concentrations within tent

2 With manifestations of backward failure particularly pulmonary edema inject a mercurial diuretic preferably thiomerin in the dose of 1 to 2 cc subcutaneously Do not give mercurial intravenously!

3 If cardiac irregularity appears to contribute to backward failure attempt to restore sinus rhythm with quinidine sulfate 0 3 to 0 6 (5 to 10 grains) every three or four hours as tolerated

4 Try to withhold digitalization until effects of the mercurial diuretic and quinidine have been observed Try to limit use of digitalis to those patients with backward failure and auricular fibrillation Unless symptoms are of great urgency avoid parenteral injection if possible Slowly digitalize with moderate doses such as 0 6 gm (10 grain) of the leaf on first and second days 0 3 gm (5 grain) on third and fourth days and 0 1 gm (1½ grain) thereafter for maintenance (p 859) In the rare instance where rapid digitalization is required dilute 0 5 mg (1/120 gr) of digoxin with 10 cc of saline and slowly inject intravenously

5 If complicating disturbance is a cerebral embolization manage as outlined

6 Reduce tempo of convalescence considerably as compared to uncomplicated coronary occlusion Maintain bed rest for six weeks to three months Do not permit any significant return to activity for a minimum period of one year observing all prophylactic precautions previously outlined (p 4583)

THYMOL

Thymol is a phenol previously used as an anthelmintic in uncinariasis (p 1903) Because of its toxicity (p 1897) it has yielded preference to tetrachlorethylene hexylresorcinol and carbon tetrachloride

Available Product

Thymol U S P Gelatin Capsules 300 mg

Occasionally the organism is recovered from blood bone marrow cerebrospinal fluid or sputum

9 The following classification is suggested by Frankel (J A M A 140 374 1949)

A Acute Toxoplasmosis Generalized irrespective of age or mode of infection involving all viscera including central nervous system diagnosed by demonstration of organisms and by rise in complement fixation and neutralizing antibody titers

B Subacute Toxoplasmosis Depending on persistence and proliferation of toxoplasma in the central nervous system including the eye subsidence of other visceral lesions due to antibody formation zone of antigen antibody reaction surrounding ventricles diagnosed by isolation of toxoplasma antigenic test with ventricular fluid and by rises in neutralizing antibody and complement fixation titers

C Chronic Toxoplasmosis Depending on persistence of toxoplasma pseudocysts in the central nervous system eye and myocardium diagnosed clinically by immunologic and serologic tests

10 Sulfapyridine sulfamerazine and sulfadiazine have been tried with beneficial results

11 Tried but found wanting were trypaflavine rivanol potassium antimony tartrate mapharsen quinine streptomycin penicillin chloroquine aureomycin polymyxin chlorguanide subtilin bacitracin p aminobenzoic acid nicotinic acid and nitrofurazine

12 Untried but worthy of trial are suramin sodium thio arsenites chloroquine and p arseno ophenylbutyric acid

13 Because many manifestations of chronic toxoplasmosis suggest hyper ensitization Frankel attempted desensitization by graded increasing doses of toxoplasma antigen (University of California Medical School San Francisco (22) Calif) supplemented by nonspecific therapy with intravenous typhoid vaccine in some instances

TRACHOMA

Principles of Diagnosis and Therapy

1 Few non fatal diseases have caused the amount of suffering and disability inflicted by trachoma (p 1625)

2 Despite its high prevalence along the eastern Mediterranean trachoma also occurs in the United States in a zone that reaches from the Alleghenies to Kansas and Oklahoma and includes eastern Kentucky Tennessee Virginia West Virginia southern Illinois southern Indiana and the Carolinas It is estimated that 10 per cent of American Indians have trachoma easily recognized by clinical observation (Fig 321 p 1625)

3 Although trachoma is caused by a virus it responds to sulfonamides and penicillin both of which will probably be replaced by

4 Trials with antimalarials (chlorguanide and chloroquine) anti protozoals (suramin sodium and p arsenosophenylbutyric acid) and amebacides (thioarsenites) merit consideration in view of lack of enthusiasm for other anti infectives

TOXOPLASMOSIS

Principles of Diagnosis and Therapy

1 Toxoplasmas are generally regarded as protozoan parasites although their exact classification is not yet definitely determined

2 Dogs cats rats sheep guinea pigs and many birds are natural hosts for toxoplasma in the U S

3 In fresh preparations toxoplasmas appear as distinct sharply outlined crescentric organisms measuring 4 to 7 microns in length and 2 to 4 microns in width The cytoplasm is clear and there is well defined nuclear chromatin In Wright stain the cytoplasm is pale blue while the chromatin is dark red to purple Toxoplasmas have an affinity for fixed cells particularly those of the reticulo endothelial system

5 The disease is most often seen in infants the infection occurring at birth or shortly thereafter (p 535)

6 Essential clinical findings are neurologic as tabulated below

	Present %
Internal hydrocephalus	80
Muscular twitching	71
Convulsions	67
Spasticity	54
Opisthotonos	45
Retraction of head	36
Stiff neck	22
Paralysis	18
Xanthochroma	05

7 Extraneurologic manifestations as noted in eighteen patients included the following

	Present %
Splenomegaly	50
Hepatomegaly	64
Jaundice	42
Purpuric spots	33
Feeding difficulty	64
Diarrhea	31
Vomiting	43
Upper respiratory infections	45
Pulmonary signs	73
Fever	60
Subnormal temperature	54

8 The diagnosis of toxoplasmosis is made by demonstration of neutralizing antibody and by finding invading organisms in tissue slides

the relapsing fevers (Bo recurrentis) spirochetal jaundice (Leptospira icterohemorrhagica) and rat bite fever (Spirillum minus)

The treponematoses all yield to penicillin though the responses are variable Additionally aureomycin and chloramphenicol have tre ponemicidal capacity These newer and less toxic antibiotics may replace organic trivalent arsenicals as products of second choice to penicillin

TRICHINOSIS

General Principles of Diagnosis and Treatment

1 Like filariasis and allied disorders (p 4327) trichinosis repre sents a systemic helminthic infection (p 539)

2 The diagnosis is established by demonstration of ova in urine or stools (Fig 90 p 540) and by demonstration of skin sensitivity to tri chinella extract (Fig 91 p 541)

3 Until recently therapy has been completely discouraging With successful treatment of filariasis using hetrazan encouraging results have also been reported with this new drug in trichinosis

4 Effective doses of hetrazan are accomplished by giving a single 50 mg tablet thrice daily for at least three weeks As in filariasis it is suggested that antihistamine be administered concurrently as 200 mg of pyribenzamine or benadryl each day

5 The toxic symptoms of hetrazan are negligible and include only slight headache malaise nausea vomiting and an occasional toxi coderm Treatment may be repeated after a holiday of ten days to two weeks

TRICHOMONAS ENTEROCOLITIS

General Principles of Diagnosis and Therapy

1 Trichomonas enterocolitis is recognized by the presence of Tri chomonas hominis in feces (Fig 651 p 2596)

2 If the patient gives a history of recurring diarrhea possibly related to the presence of Trichomonas institute therapy with tri chomonicide (p 4592) preferably carbarsone Order tablets of 250 mg twice daily for ten days At the end of this time reexamine stools If organisms persist repeat therapy after a rest period of ten days to two weeks

3 In the instance of arsenic resistant Trichomonas enterocolitis suggest a course of aureomycin of 50 mg per kilogram of body weight (4 products four times daily for the average adult weighing 150 lbs)

aureomycin which appears to be spectacularly specific (Braley and Sanders Ann New York Acad Sc 51 280 and J A M A 138 426 1948)

Practical Management

1 Into each eye instill 2 or 3 drops of aureomycin ophthalmic solution prepared by dissolving 25 mg in the diluent provided by the manufacturer

2 Into the lid margin rub aureomycin hydrochloride ophthalmic ointment

3 Because of the grave consequences of the disease supplement local with systemic aureomycin therapy Give a priming dose of 25 mg per kilogram of body weight (1 75 gm for average adult weighing 150 pounds) Maintain antibiotic levels with a daily dose equal to priming dose but divided into 4 equal portions given at 6 hour intervals To prevent gastric irritation wash antibiotic down with water fruit juice tea milk or ice cream Continue therapy for a minimum period of ten days to prevent chronic deformities resulting in impairment of vision (p 1626)

4 Despite their efficacy local and systemic soluble sulfonamides are now obsolete (Murray Canadian Med Assn J 60 574 1949) Similarly penicillin yields preference to aureomycin chloramphenicol Completely abandoned are drastic methods of local therapy including application of silver nitrate to the lids and cauterization with copper sulfate

TRENCH FEVER

[Wolhynian Fever His Werner Disease Five Day Fever Meuse Fever Shank Fever Shin Fever]

Principles of Diagnosis and Therapy

1 Trench fever is a specific benign rickettsemia that involved at least 1 000 000 soldiers in World War I The infection has no mortality

2 The specific invader is transmitted by pediculi

3 The diagnosis is made epidemiologically since the disease has no specific clinical features or laboratory findings (p 383)

4 Prophylaxis is accomplished by pediculocides (p 4446)

5 As in the case of other invasions of similar origin trench fever merits probatory antibiotic therapy with aureomycin chloramphenicol and/or para aminobenzoic acid as given in typhus (p 4621)

TREPONEMATOSES

[Spirochetoses]

The treponematoses include syphilis (Tr pallidum) frambesia (Tr pertenue) pinta (Tr carateum) fusospirochetosis (Bo vincenti)

5 Subject the sexual partner to local treatment if Trichomonas are demonstrable in prostate secretion urethra or under the prepuce If the preputial cavity is accessible local therapy can be accomplished by retraction and painting with 1% gentian violet Otherwise circumcision is suggested (p 3936)

6 Gynecologic defects in the female require surgical correction i e excision of Skene s or Bartholin glands or repair of cervix

7 For home treatment the patient is required to take douches with products that have no potential for toxicity Thus a solution of one half to two tumblerfuls of table salt dissolved in 2 quarts of water produces local conditions hostile to growth of Trichomonas Similarly douches of 2 to 4 tablespoonfuls of white vinegar or of 1 to 4 teaspoonfuls of lactic acid U S P (4 to 16 cc) to 2 quarts of water produce an acid vaginal secretion unpalatable to Trichomonas Douches are best taken in the morning and again on retiring

8 For self medication patients insert preparations of minimum toxic potential Thus initial trial is suggested with aci-gel, marketed with a convenient vaginal dispenser allantoin cream or oxyquinoline preparation such as vioform or floraquin The two last are supplied as vaginal tablets inserted one in the anterior and one in the posterior fornix twice daily for a period of at least six weeks including the time of menstrual flow Vaginal suppositories of ceepryn (1 1000) also are available and may be given safely for self medication

9 In resistant Trichomonas infection resort to arsenicals such as vaginal suppositories of carbarsone

10 In addition to self treatment the patient reports to the office for insufflations particularly during the menstrual flow The physician has choice of oxyquinoline derivative such as vioform preparations of picric acid such as 1% silver picrate or arsenicals such as acetarsone or devegan Each of these preparations is supplied in vaginal powder for insufflation to be used after thorough cleansing of the vaginal cavity and scrubbing of folds with green soap using cotton on a dressing forceps

11 The patient is warned of possible recurrence particularly after the menstrual flow She is cautioned to continue home treatment after each period and return for office examination and treatment if necessary at least monthly for several months

TRICHURIASIS

[Whipworm Infestation]

Principles of Diagnosis and Therapy

1 The diagnosis of trichuriasis is dependent on recognition of ova in stools (Fig 1099 p 3730)

2 Infestations are limited to local manifestations Systemic invasion does not occur

TRICHOMONICIDES

Product	Comment
Acetar one N F (Abbott)	Pentavalent arsenical available in 12 5% powder for insufflation Prefer potentially less toxic products
Aci Jel (Ortho)	Jelly buffered to pH 4 0 Marketed with intravaginal applicator Non toxic and acceptable for trial
Allantoin (National)	In 2% ointment or vaginal cream Merits trial
Arsenicals	Pentavalent acetarsone aldarsone carbarsone devegan and phenarsone are available Prefer potentially less toxic products
Carbarsone U S P (Lilly)	Pentavalent arsenical available in vaginal suppositories containing 0 13 gm or in powder Prefer potentially less toxic products
Ceepryn (Merrell)	Quaternary ammonium salt available as 0 5 % powder or 1 1000 vaginal suppository Non toxic and merits trial
Devegan (Winthrop)	Arsonic acid derivative available in tablets or powder Prefer potentially less toxic products
Floraquin (Searle)	An oxyquinoline derivative available in powder or tablets for intravaginal insertion Non toxic and merits trial
Lactic Acid U S P	*For producing an acid vaginal flora Use as douche beginning with 4 cc (1 teaspoonful) to two quarts of water Increase gradually to 16 cc (4 teaspoonfuls)*
Picragol (Wyeth)	Silver picrate in 1% powder Prefer less irritating products which do not sting
Salt	*Add a tumblerful of table salt to two quarts of water Increase to two tumblerfuls if tolerated*
Stovarsol (Merck)	See acetarsone
Vinegar	*To lower acidity of vaginal flora start with two to four tablespoonfuls of white vinegar per two quarts of water Increase strength as tolerated*
Vioform N N R (Ciba)	An oxyquinoline derivative available in vaginal inserts or powder for insufflation Merits trial

TRICHOMONAS VAGINITIS

General Principles of Diagnosis and Therapy

1 Trichomonas vaginitis (p 2598) is very common in office practice The diagnosis is established by identification of unstained protozoans under the microscope in fresh preparations obtained through a vaginoscope that has not been lubricated (Figs 651–654 p 2596)

2 The many effectual trichomonicides are listed in the accompanying chart (p 4592)

3 Preliminary to specific therapy examine patient and sexual partner Nests of the protozoan may be found in cervix Skene s glands Bartholin glands urethra prepuce prostate anus and rectum As in the diagnosis of vaginitis identification of Trichomonas is easily accomplished by making a fresh saline spread of feces and examining immediately under the microscope

4 Whether or not the patient has demonstrable trichomonas in the stool she is instructed concerning rectal hygiene The anus must be wiped from before backward and not forward soiling vagina with fecal content

TRYPANOCIDES

Preparation	Comment
Acriflavin	Obsolete coal tar derivative
Antrycide (M 7555)	A British synthetic product under experimental investigation Not commercially available (p 4227)
Atoxyl	Obsolete toxic arsenical
Bayer 7602	Superseded by uramin for its lesser toxicity Used intramuscularly in doses of 5–20 cc of 3% solution to total 200–250 cc for average sized adult with Chagas disease
Neocryl	A trivalent proprietary arsenical not available in America Used in weekly doses of 2–4 gm
p Arsenosophenylbutyric Acid	An arsenical currently used experimentally by the United States Public Health Service (p 4233)
Stilbamidine	An aromatic diamidine of antimony (p 4225) under experimental investigation but certainly much more toxic than suramin
Suramin Sodium U S P (Antryptol Bayer 205 Fourneau 309 Germanin) Naphuride Urea)	A urea derivative that is highly efficacious and only mildly toxic commercially available currently the preparation of choice (p 4553)
Trypaflavin	An active flavin derivative introduced by Ehrlich Not very efficacious superseded by suramin
Tryparsamide (Fourneau 270)	A pentavalent organic arsenical highly toxic and by no means as effectual as formerly believed Now obsolescent
Urea	See uramin

Immediate Care

1 Inaugurate measures used for control of infectious disease (p 68)

2 Inject intravenously 10 cc of a freshly prepared 10% solution of sodium suramin made by dissolving contents of ampul containing 1 gm of naphuride odium (Winthrop) in sterile distilled water or physiologic saline Sprinkle powder on surface of diluent to prevent clumping (p 4553)

Continuing Care (Unfavorable Course)

1 Request the United States Public Health Service to furnish p arsenosophenylbutyric acid Supplement suramin with a course of 12 to 14 daily injections The preparation is non toxic and is trypanosomicidal

2 If p arsenosophenylbutyric acid is not obtainable supplement suramin sodium with tryparsamide (Fourneau 270) particularly with signs of invasion of the nervous system Give probatory intravenous injection of 0 5 gm dissolved in sterile distilled water If tolerated give 3 gm once or twice weekly for twelve weeks Discontinue immediately if any toxicity appears (agranulocytosis leukopenia amblyopia contraction of visual or color fields blurring of vision photophobia or lacrimation) Start antidotal treatment with BAL (p 4251)

Continuing Care (Progressively Unfavorable Course)

1 Suramin and arsenicals failing try antimony u ing pentamidine (M & B 800) if available Inject 100 mg dissolved in 10 cc of distilled water daily for twelve days

3 Treatment is conducted as for ascariasis For immediate care use suggestions incorporated in paragraphs 2 3 and 4 (p 4240)

4 For continuing care of unfavorable course follow suggestions of paragraphs 2 and 3 of resistant infestation with ascaris (p 4240)

TRYPANOSOMIASIS

(African Sleeping Sickness South American Sleeping Sickness Chagas Disease Nagana)

Principles of Diagnosis and Treatment

1 Trypanosomiasis is a protozoal infestation transmitted to man by the tsetse fly (Fig 88 p 532)

2 Clinical subvarieties of trypanosomiasis are recognized in tropical Africa (Gambian) Rhodesia (Rhodesian) and South America (Chagas disease) (pp 531–532)

3 Of the subgroups Chagas disease is most resistant to therapy In its chronic form it is prone to produce cardiac manifestations

4 Modern medicine has now effectual tools for prevention and possible cure

5 The problem of trypanocides has broad political implications in addition to its obvious medical importance Conquest of the continent of Africa is more or less dependent upon control of trypanosomiasis in man and in animals For this reason as indicated by the complicated nomenclature English French and German investigators have experimented with secret formulas to the confusion of all genuinely interested in conquest of the microbic invader Much of the credit for present simplification is due to Eagle and his associates in the United States Public Health Service who have prepared suramin sodium as well as p arsenosophenylbutyric acid

Practical Management

Prophylaxis

1 Clear milewide strips of jungle to prevent migration of flies which cannot travel more than a few hundred feet without resting

2 Sacrifice infected wild animals

3 Treat domestic animals with antrycide (p 4227)

4 Use insect repellents especially at mid-day when flies bite

5 Inject 1 gm of sodium suramin as for active therapy Repeat in one week and again every three months Naphuride has only minor and transitory toxicity including edema toxicoderms pruritus conjunctivitis stomatitis and peripheral neuritis

Continuing Care (Favorable Course)

1 Maintain antibiotic level by repeating the priming dose over a 24 hour period using four equal doses i e 4 products every six hours
2 Continue antibiotics for at least two days after defervescence

Continuing Care (Unfavorable Course)

1 If symptoms continue and product is well tolerated double amount of each dose and reduce time intervals to three hours
2 If symptoms continue and antibiotic is not tolerated substitute the other i e if patient is nauseated by aureomycin switch to chloramphenicol or vice versa
3 If neither product is tolerated use para aminobenzoic acid Give a priming dose of 8 gm of PABA (16 tablets of 0 5 gm each) with bicarbonate of soda Order maintenance do es of 3 gm every two hours until patient has been afebrile for two days

Continuing Care (Progressively Unfavorable Course)

1 Combine aureomycin and/or chloramphenicol in a total daily dose of 8 gm with PABA in a total daily do e of 36 gm
2 If there is gastric intolerance insert a duodenal tube and give antibiotics transduodenally
3 With continued distre s set up an intravenous drip For priming dose introduce 500 mg of aureomycin hydrochloride and alternate with 120 cc of 5% odium PABA in physiologic saline
4 Watch the blood count Introduce 500 cc of whole blood for anemia stop PABA if leukopenic give two units of plasma for toxemia or prostration
5 Prepare for long convale cence
6 Obsole cent useless or detrimental are nitroacridine 3582 rutenol sulfonamides penicillin and digitalis

TUBERCULOSIS

General Principles of Diagnosis

1 Despite a reduction of 72 per cent in mortality there were approximately 50 000 deaths from tuberculosis in the United States in 1947 The total population of the tuberculous is estimated in excess of 500 000

2 Tuberculosis does not recognize social or economic strata While the large t numbers of the tubercular admittedly are found where there is poor housing undernutrition and crowding the disease may manifest itself among the comfortably housed well fed and ocially privileged

3 In routine examination of the office population include a survey for tuberculosis make inquiries concerning familial or occupational

2 Try Bayer 7602 presently of unknown composition Inject intra muscularly 5 to 20cc of 3% solution to total 200 to 250 cc for adult weighing 150 pounds
3 Try neocryl using weekly doses of 2 to 4 gm
4 Atoxyl (sodium arsenilate) acriflavin trypoflavin tartar emetic and antimony trioxide are regarded as obsolete because of relatively feeble trypanocidal action compared with toxic potential

TSUTSUGAMUSHI FEVER

[Japanese River Fever Kedani Malaya Typhus Mite borne Typhu Rural Typhus Scrub Typhus Tropical Typhus]

Principles of Diagnosis and Therapy

1 Tsutsugamushi fever is a rickettsemia transmitted by mites and chiggers A primary lesion usually develops at site of inoculum (Fig 59 p 382) After an incubation period of four to twenty-one days systemic manifestations appear characterized by fever lymphadenopathy and a maculopapular rash (p 381)
2 Tsutsugamushi fever can be prevented and specifically treated

Prophylaxis

1 Avoid bites of vectors by use of long trousers sleeves and tight collars
2 Use insect repellent (p 4373) U S Army impregnates clothing with an emulsion containing 45 parts of benzyl benzoate 45 parts of dibutyl phthalate and 10 parts emulsifier (Scientific Monthly Nov 1943 p 288)
3 Inject specific vaccine for development of active immunity Give booster doses at least twice annually to those in exposed areas For initial inoculation introduce three 1 cc doses at weekly intervals The vaccine is not commercially available but may be obtained from the United States Public Health Service

Immediate Care

1 Inaugurate nonspecific measures of treatment of generalized infec tion (p 68)
2 Para aminobenzoic acid aureomycin and chloramphenicol are specifics in scrub typhus Either of the latter two is preferred
3 With chloramphenicol or aureomycin order a loading do e of 50 to 100 mg per kilogram of body weight For the average adult weighing 150 pounds give four equal portions at hourly intervals each of 4 products (1 gm) with milk ice cream soup or cream cheese If either preparation is not tolerated t y the other

imilar pathologic inflammation Those microbes which most frequently mimic tubercle bacilli are fungi histoplasmas toxoplasmas and helminths (p 2210)

10 The tuberculin test is not oracular It does not tell whether or not the patient is suffering from tuberculosis It does not nece sarily imply that the di ease is active Quite simply it denotes that a defensive mechanism has been set up by host tissues against the protein of the tubercle bacillus The test may be positive when the di ease is inactive and the patient is suffering from some quite different invasion Contrariwi e it may be negative in early stages of infection for it takes approximately a month to develop when artificially produced by BCG vaccine On rare occasions it is negative in the presence of virulent tubercular infection when the patient is anergic or incapable of producing antibody as in fulminating miliary and meningeal involvements and in sarcoidosis

11 Clinical and radiographic evidences of invasion by tubercle bacilli are not necessarily indicative of activity Particularly in the case of chest radiographs and palpation of tuberculous nodes the physician merely recognizes scars of a previously active infection Under these circumstances quite naturally the burden of proof is on the side of proving the innocence of the acid fast organism But even the combination of a positive tuberculin reaction and a chest radiograph showing a tuberculous lesion is not sufficient to prove that given symptoms necessarily are tuberculous

12 Demonstration of tubercle bacilli in sputum together with tuberculin positivity and demonstrable radiographic evidences of tuberculous infection also may not necessarily mean that the patient is suffering from tuberculosis Chronic spitters are a very definite menace to the community at large and to their households and fellow workers in particular but they may have reached a stalemate with the invading microbe where they themselves no longer suffer significantly from tuberculosis despite the weight of positive evidence to the contrary

13 When the proven tuberculous patient develops evidences of activity such as a rapid sedimentation rate and fever this too may not necessarily be due to tuberculosis The patient may have a positive tuberculin reaction a positive chest film tubercle bacilli in the sputum a rapid erythrocyte sedimentation rate and fever and still suffer from an unrelated superimposed infection

14 The clinical manifestations of tuberculosis are tabulated in the accompanying chart Note particularly under Cutaneous Manifestations that there is a clear differentiation between lesions due to direct implantation with tubercle bacilli (tuberculous diseases of the skin) and those due to hypersensitivity to the protein of tubercle bacilli (tuberculids) In the former acid fast bacilli are demonstrable though the search may be long and tedious in the latter tubercle bacilli cannot be demonstrated or even transmitted to experimental animals although the relationship of the given syndrome to the organism is clinically established beyond doubt

exposure to acid fast infection note suspicious subjective complaints such as malaise failure to gain weight loss of weight (p 700) anorexia (p 1779) chronic cough (p 2050) or persistent expectoration look for physical signs of cutaneous lymphatic or pulmonary involvement perform a tuberculin skin test using intracutaneous method or Vollmer patch (Fig 35 p 264 and Fig 34 p 263) insist on a routine chest radiograph (Figs 28–33 pp 255–260) obtain a record of rectal temperatures taken at least twice daily for a week (p 3484)

4 If specimens are obtainable make direct carbol fuchsin stains of sputum urinary sediment gastric contents stool cerebrospinal fluid or biopsy material (Fig 6 p 29)

5 Resort to *Petroff concentration* technic when direct examinations are negative in the presence of suggestive clinical manifestations Instruct patient to reject saliva and only expectorate into the sterilized vessel material brought up from the bronchi Keep sputum until there is a total quantity in excess of 15 cc

To concentrate sputum specimen mix in a flask with equal parts of chlorox a commercial bleaching agent Shake 2 or 3 times over a 2 minute period Keep at room temperature for ten minutes before transference to a 15 cc centrifuge tube with a conical tip Centrifuge at 300 r p m for ten minutes Decant supernatant fluid and drain for two minutes Place a small drop of sediment on a slide and make a moderately thin smear Stain with carbol fuchsin according to the Ziehl Neelsen method (p 52)

6 In infancy and childhood when sputum is swallowed examine gastric contents

Wash a Levine tube (p 1751) in hot water and soap rinse with tap water for thirty minutes boil in a weak solution of sodium carbonate for another half hour and place in the refrigerator overnight In the morning pass tube intranasally before breakfast aspirate at least 5 cc of gastric content with a Luer syringe mix with an equal volume of digestant consisting of 1% sodium hydroxide 0 2% potassium alum and 0 002% brom thymol blue place in water bath at 37 C for thirty minutes shaking occasionally add dropwise 2 5 cc of N/1 hydrochloric acid and shake for thirty seconds after indicator turns blue (pH 7 6) If flocculation does not occur in less than five minutes add 0 2 cc of 1% ferric chloride Shake again until flocculation does occur and then centrifuge at high speed for five minutes Decant supernatant fluid and prepare slides from sediment Dry in air and stain by Ziehl Neelsen method (p 52)

7 Swallowed tubercle bacilli retain staining characteristics despite passage through the digestive tract If sputum and gastric content cannot be obtained suspend a specimen of feces concentrate and examine as indicated above

8 If tubercle bacilli are not demonstrable by staining methods try animal inoculation

Centrifuge suspected material decant supernatant fluid inject at least 2 cc of sediment into peritoneal cavity or underneath loose skin of the groin of several guinea pigs carefully house and isolate animals after eight weeks sacrifice them and look for characteristic pearl gray or yellow tubercles in areas of injection crush suspected material between slides dry and stain as previously described

9 In non tuberculous chronic pulmonary infections suspect pathogenic participation of some other organism capable of producing

similar pathologic inflammation Those microbes which most frequently mimic tubercle bacilli are fungi histoplasmas toxoplasmas and helminths (p 2210)

10 The tuberculin test is not oracular It does not tell whether or not the patient is suffering from tuberculosis It does not necessarily imply that the disease is active Quite simply it denotes that a defensive mechanism has been set up by host tissues against the protein of the tubercle bacillus The test may be positive when the disease is inactive and the patient is suffering from some quite different invasion Contrariwise it may be negative in early stages of infection for it takes approximately a month to develop when artificially produced by BCG vaccine On rare occasions it is negative in the presence of virulent tubercular infection when the patient is anergic or incapable of producing antibody as in fulminating miliary and meningeal involvements and in sarcoidosis

11 Clinical and radiographic evidences of invasion by tubercle bacilli are not necessarily indicative of activity Particularly in the case of chest radiographs and palpation of tuberculous nodes the physician merely recognizes scars of a previously active infection Under these circumstances quite naturally the burden of proof is on the side of proving the innocence of the acid fast organism But even the combination of a positive tuberculin reaction and a chest radiograph showing a tuberculous lesion is not sufficient to prove that given symptoms necessarily are tuberculous

12 Demonstration of tubercle bacilli in sputum together with tuberculin positivity and demonstrable radiographic evidences of tuberculous infection also may not necessarily mean that the patient is suffering from tuberculosis Chronic spitters are a very definite menace to the community at large and to their households and fellow workers in particular but they may have reached a stalemate with the invading microbe where they themselves no longer suffer significantly from tuberculosis despite the weight of positive evidence to the contrary

13 When the proven tuberculous patient develops evidences of activity such as a rapid sedimentation rate and fever this too may not necessarily be due to tuberculosis The patient may have a positive tuberculin reaction a positive chest film tubercle bacilli in the sputum a rapid erythrocyte sedimentation rate and fever and still suffer from an unrelated superimposed infection

14 The clinical manifestations of tuberculosis are tabulated in the accompanying chart Note particularly under Cutaneous Manifestations that there is a clear differentiation between lesions due to direct implantation with tubercle bacilli (tuberculous diseases of the skin) and those due to hypersensitivity to the protein of tubercle bacilli (tuberculids) In the former acid fast bacilli are demonstrable though the search may be long and tedious in the latter tubercle bacilli can not be demonstrated or even transmitted to experimental animals although the relationship of the given syndrome to the organism is clinically established beyond doubt

CLINICAL MANIFESTATIONS OF TUBERCULOSIS

Involved Structure	Text Page	Figure
CUTANEOUS		
Tuberculous Dermatoses		
Chancre	3258	
Verrucosa Cutis	3259	
Scrofuloderma	3262	951 p 3263
Ulcers	3262	
Lupus Vulgaris	3262	951 p 3263
Tuberculids		
Lichen Scrofulosorum	3269	
Papulonecrotic	3270	
Lupus Miliaris Faciei	3270	952 p 3263
Rosacea-like (Lewandowsky)	3270	
Erythema Induratum	3271	953 p 3263
Sarcoidosis	3271	954 p 3263
RESPIRATORY		
Laryngeal	2161	493–495 p 2162
Acute Miliary	261	27 p 254
Acute Bronchopneumonic	2189	
Acute Pneumonic	2189	
Primary Complex	258	28–29 p 255 30 p 256 31 p 257
Prephthisical	259	32–33 p 260
Chronic Pneumonic	2199	26 p 253 500 p 2200 501 p 2204 502 p 2208
Pleural	257	
DIGESTIVE		
Oral	1672	343 p 1671
Intestinal	1860	416 p 1861
Peritoneal	1930	417 p 1861
ENDOCRINE		
Adrenal (Addison's Disease)	1272	
NEUROLOGIC		
Meningeal	267 1462	
Ocular	1603	276 p 1464 316 p 1604
GENITAL		
Penile	2455	
Seminal Vesicular	2468	
Epididymo Orchitic	2462	
Prostatic	2472	
Vulvar	2588	
Uterine Cervix	2602	
Salpingo-oophoritic and Endometritic	2610	660 p 2610
Mastitic	2613	

CLINICAL MANIFESTATIONS OF TUBERCULOSIS (*Continued*)

Involved Structure	Text Page	Figure
URINAPY		
Urethral	2337	
Renal	2347	561 p 2347
		~62 p 2348
		~63 p 2349
LOCOMOTOR		
Hip	2942	768 p 2944
Knee	2945	769 p 2944
Spinal	2962	767 p 2963
Ankle		770 p 2945
Carpal		771 p 2946

15 Quite likely differentiation between tuberculous lesions and tuberculids is relative rather than absolute Probably there are hyper ensitivity manifestations in most patients actively infected with tubercle bacilli certainly hyper~ensitivity manifestations predicate prior bac terial invasion of host tissues

16 The practical significance of the e observations is currently trans latable into the realities of therapeutics Tuberculocidal preparations may be accounted valuable in the treatment of lesions due to invasion by acid fast organi ms Quite obviously however they cannot be expected to dissipate manifestations of hypersensitivity On the other hand antihistamines and preparations possessed of adrenocortical or adrenocorticotropic activity obviously impotent tuberculocides have therapeutic potential in the prevention and relief of those inflammatory phenomena that are due to hypersensitivity of host tissues to tuber culoprotein

17 Even these limited considerations of problems in the diagnosis of tuberculosis indicate the complexity of clinical problems presented to the practitioner In any given situation the following questions arise

(a) Does the patient suffer from tuberculosis?
(b) Is the lesion an invasive inflammatory process or is it a hyper sensitivity manifestation?
(c) What is the degree of activity?
(d) Are pre enting symptoms related to acid fast invasion or are they merely co incidental?

18 While each individual case must be decided on its merits cer tain general guiding principles are definitively established

(a) *Demonstration of tubercle bacilli definitively establishes that the* patient is tuberculous
(b) The presence of a positive tuberculin reaction indicates that host tissues have become sensitized to the protein of the tubercle bacillus
(c) The a ociation of demonstrable bacilli and a positive tuberculin reaction indicates that the patient has experienced invasion and resultant hypersensitivity
(d) The patient who reveals evidences of tuberculous invasion and/or sensitivity to cutaneously introduced tuberculin but has

neither subjective nor objective evidences of activity (normal temperature curve and normal erythrocyte sedimentation rate) may be regarded as one who has suffered infection become sensitized and built up an adequate immunological defense mechanism

(e) That patient who presents evidences of invasion by tubercle bacilli and sensitization to protein of the invading organism and who has additional signs of activity (constitutional symptoms elevation of temperature and increased erythrocyte sedimentation rate) must be regarded as suffering from tuberculosis until the contrary is proven remembering always that the tuberculous patient may suffer intercurrent diseases in the same manner as the non tuberculous

GENERAL PRINCIPLES OF PROPHYLAXIS

Tuberculosis control programs (exclusive of vaccination) have reduced the death rate in the United States in the past forty years from 200 to 36 per 100 000 population (72 per cent)

During the same period Denmark effected a reduction in mortality *from 300 to 32 per 100 000 population (89 per cent)* using both segregation and immunization If the Danish experience were duplicated in the United States addition of BCG vaccination to current prophylactic measures might conceivably result in an annual saving of 9 000 lives

BCG Vaccination

BCG vaccine an attenuated suspension of living tubercle bacilli was originally obtained from growths of a non virulent bovine organism isolated from the milk of a tuberculous cow by Calmette and Guerin in 1906 The Bacillus Calmette Guerin has suffered further reduction in virulence through repeated transfers on artificial media As a result inoculations with avirulent Calmette Guerin strain produce only local nodular lesions without progression or generalization of the infectious process Vaccinated animals later infected with virulent tubercle bacilli are capable of resisting progressive infection to a very great extent

In 1931 Petroff dissociated BCG into rough R and smooth S form The latter had the capacity to produce progressive disease in animals Rosenthal (working in an isolated laboratory where only BCG was cultured and using many thousands of cultures) demonstrated that BCG was a pure R form and as such incapable of producing progressive tuberculosis This viewpoint later conceded by Petroff has been verified by the fact that Rosenthal in an experience that now covers more than thirteen years has never seen progressive disease following BCG inoculation in any phase He has injected into animals 300 000 times the human dose calculated by weight without producing deleterious effects

One of the major disasters in tuberculosis vaccination occurred in Lubeck (Germany) where 77 of 271 infants given BCG vaccine by mouth died of progressive disease Koch acting for the German government proved that Lubeck vaccine was a mixture of BCG and a virulent strain of tubercle bacilli kept in the same incubator as the avirulent product The virulent strain received from the nearby town of Kiel was readily identified by its phosphorescent green color in Sauton medium The use of this virulent strain was regarded, by the investigator as criminal and those responsible were imprisoned for an act of malpractice

BCG vaccine has not yet been licensed for commercial production in the United States of America However vaccine may be obtained by responsible physicians, through application to the Tuberculosis Control Division of the United States Public

Health Service the Tice Laboratory of the Chicago Municipal Tuberculosis Sanitarium, the Henry Phipps Institute of Philadelphia and the University of Illinois

BCG may be introduced by intracutaneous injection, or by the method of multiple puncture *Intracutaneous injection* is recommended by Aaronson who uses a single introduction, into the arm, of 0 1 or 0 15 mg of freshly prepared BCG vaccine suspended in physiologic saline solution

After forty-eight hours intracutaneous injection is followed by development of a sharply defined nodule measuring about 4 mm in diameter and surrounded by a small halo of redness During the next two weeks the local inflammatory reaction decreases but the nodule gradually increases in size

Three to four weeks after vaccination the nodule undergoes a rapid increase in size At this time the patient usually complains of dull ache at the site of injection, and there is observed a central area of softening Simultaneously axillary lymphadenopathy is palpable accompanied by sensitiveness but not pain

Eight to twelve weeks after vaccination, the majority of nodules and their satellite lymph nodes shrink and leave only a soft local scar at the site of inoculation. This may persist for many years

In an extensive experience Aaronson reports that none of the lymph nodes ulcerated. Only occasionally did a nodule break down leaving an ulcer which later healed. No untoward local or general reactions were observed by this investigator following vaccination and surgical intervention was never required

The *multiple puncture method* is recommended by Rosenthal. His preparation (made at the Tice Laboratory of the Chicago Municipal Tuberculosis Sanitarium, and at the University of Illinois College of Medicine) is harvested from a synthetic medium (Sauton) suspended in a buffered saline solution, and put up in capillary tubes in much the same way as is done for vaccine virus

Rosenthal rejects the oral method, originally advocated by Calmette and later used by Weil Halle He objects to the intracutaneous route on the basis of local ulcerations which may persist for months with formation of abscesses and suppuration of axillary lymph nodes

The multiple puncture method of Rosenthal according to the originator of this technic is completely free from complications In his own words the technic of inoculation is as follows

A drop of vaccine is placed on the outer aspect of the alcohol-cleansed arm A sewing type needle similar to the one used for vaccinia, is held between the thumb and the index finger about 1 5 cm from the point The thumb and needle should form a continuous line With the shaft of the needle held tangentially to the skin the vaccine is spread in linear fashion for a distance of 2 5 cm By a downward pressure exerted to a large extent by the thumb the skin is pierced with the needle point through the vaccine Following this downstroke which engages the point of the needle into the skin an upward movement is exercised without disengaging the needle The point of the needle remains buried in the skin on the upstroke This precaution makes the method fool proof The punctures are placed about 2 to 4 mm. apart, and ten punctures are made in a line The vaccine is spread to the second line parallel to the first and 4 to 6 mm away Thus three lines of ten punctures each are made in an area of approximately 2 5 by 1 5 cm The vaccine is allowed to dry on the arm, no blotting or covering with dressings is practiced Wetting of the arm should be avoided for twenty four hours

The lesions following the multiple puncture method in newborn infants resemble goose flesh for two to six weeks following vaccination In children and adults each puncture progresses to form pink papules from a pinhead to 3 mm. in size These papules after four to eight weeks regress rapidly The recipient is usually unaware of which arm was scarified The draining lymph nodes may be palpable two weeks after vaccination but never enlarge to the extent that the recipient is aware of it. Ulceration and breaking down of lymph nodes have never been seen. (J A M A 136 75 1948)

The *results* of the BCG vaccination have been tabulated both by Aaronson using the intracutaneous method and by Rosenthal who employed his technic of multiple puncture.

Aaronson in a study of 3 000 inoculated American Indians observed 1457 unvaccinated controls In the control group 52 died of tuberculosis and, after a span of eleven years only 39 per cent spontaneously developed a positive tuberculin reaction By contrast

in the 1550 who were vaccinated there were but six deaths from tuberculosis of the survivors 91 per cent were tuberculin positive after eleven years of observation. In other words the percentage of deaths in the vaccinated group was reduced to 11 per cent as compared to the controls and of the survivors the vaccinated group included more than double the number of tuberculin positive presumably protected individuals

In Rosenthal s experience with 2 831 newborn infants living in the poorest district of Chicago but not in household contact with tuberculosis there were eleven cases of tuberculosis in the vaccinated as against thirty nine in the controls there was one fatality in the vaccinated group against seven in the control group In 1 159 siblings of the tuberculous the tuberculosis rate per thousand person years was 5 29 times as great in controls as in the vaccinated In 256 new born infants living in tuberculous homes there were two cases of tuberculosis in the vaccinated as compared to five in the controls None of the vaccinated children died whereas there were four deaths in the control group

By the method of multiple puncture tuberculin reaction conversion is rapid occur ring within one month in virtually all of those observed A positive tuberculin reaction, following a single vaccination persisted in 92 6 per cent for approximately four years and in 80 per cent after six years

Opponents of BCG vaccine no longer sustained by the Lubeck experience or by Petroff s subdivision into R and S strains offer the following reasons for circumspection in considering BCG vaccination

Knowledge of tuberculosis immunity is inadequate to justify artificial immunization with living organisms

BCG has failed to immunize animals effectively

Convincing proof of the value of BCG vaccination is still lacking after a quarter century of use and administration to approximately 7 million persons

BCG vaccination must be regarded as experimental Its use should be controlled and limited in order to prevent fostering a false sense of security that would lead to neglect of fundamental procedures

Proof that BCG is harmless is not absolute Though inoculation is apparently not immediately dangerous organisms may survive for years and gradually regain virulence

Favorable reports with rare exceptions have been from inadequately controlled studies

Diagnostic criteria can be questioned in most of the cases upon which favorable reports are based

Technics similar to Calmette s method have been tried and discarded All started from the same shaky premises namely that dependable immunity is not produced by an actual attack of tuberculosis

The tuberculin skin test a potent weapon against tuberculosis is nullified if tissues are sensitized with BCG administered to a considerable number of the nation s chil dren and adults

BCG does not prevent virulent tubercle bacilli from entering the human body nor does it destroy them

Because of the many conflicting views with regard to BCG a con ference held under the auspices of the United States Public Health Service met in Washington on September 7 1946 (Public Health Reports 62 346) At this time the following conclusions and recom mendations were established

1 Medical literature fails to reveal any proven cases of progressive disease as a result of BCG vaccination

2 From studies presented at the conference it appears that BCG vaccination con fers increased resistance to tuberculosis for the limited period of time covered in these studies

3 Extensive investigation should be carried on cooperatively with recognized

research groups throughout the country during the coming years especially in population groups highly exposed to tuberculous infection.

4 It is recommended that a single laboratory be established by the Tuberculosis Control Division to produce BCG Vaccine for the whole of the United States for use in research programs as proposed at the conference

While the entire subject of BCG vaccination is in the experimental stage several definitive policies appear to have evolved particularly as the result of the Washington Conference of 1946 In general the following conclusions appear acceptable to most authorities

1 Under ordinary conditions with proper housing adequate diet modern hygienic advantages and non-contact with tuberculous individuals in family household or occupation there is no need for universal BCG vaccination in the United States of America

2 In less favored countries where the population cannot be guaranteed dietary domiciliary and hygienic advantages of a modern civilization and where there is a high incidence rate of tuberculosis mass BCG vaccination of non reactors merits serious consideration This principle has been implemented by the World Health Organization a subdivision of United Nations in many devastated countries and localities

3 Individual BCG vaccination of non reactors by the general practitioner may be required in the United States under special circumstances These include heavy exposure to tuberculosis as in infants born of tuberculous parents children and marital partners of the tuberculous students nurses physicians and personnel exposed to the disease in the pursuit of professional activities occupants of large housing units such as asylums jails dormitories and perhaps the barracks of the armed forces and those who without excessive exposure to tuberculosis are exposed to unhygienic conditions through inadequate diet improper housing crowding and inclement weather conditions

4 In some Scandinavian countries where the population is more compact and there is a greater consciousness of public health measures BCG vaccination appears more favored Thus in the Swedish army all non reactors are inoculated In Norway there is a bill making inoculation compulsory In Denmark more than 100 000 people were vaccinated in 1946 and the newly constituted government of India is considering nation wide inoculation In the United States there is an American Indian project embarked on by the government as the result of the high susceptibility of this group to tuberculosis

GENERAL PRINCIPLES OF THERAPY

1 Having established the tuberculous etiology of presenting clinical manifestations determined the nature of the inflammatory process whether infectious allergic or both and estimated the degree of activity of the lesions the practitioner next is confronted with the equally intricate problem of devising a therapeutic program

2 Available therapeutic procedures include non specific measures of general hygiene surgical intervention and prescription or administration of tuberculocide and antiallergens For integration of the entire program an initial roundtable consultation with phthisiologist and thoracic surgeon is highly recommended

3 Emphasis on specific therapeutic devices must not overshadow non specific measures These latter include bed rest at home or in the sanitarium climatotherapy dietotherapy heliotherapy psychotherapy, bibliotherapy and occupational therapy (pp 267–272)

4 Surgical procedures may be indispensable to recovery in tuberculosis They include *induction of pneumoperitoneum or pneumothorax* (p 2033) crushing or avulsion of the phrenic nerve (p 2039) intrapleural pneumolysis thoracoplasty (p 2040) pneumonectomy or lobectomy (p 2039) unilateral nephrectomy or excision of infected testes epididymes tubes ovaries and lymph glands

5 For pharmacotherapy the practitioner has a variety of tuberculocidal preparations as tabulated in the accompanying chart Currently streptomycin para aminosalicylic acid and thiosemicarbazones hold greatest promise for good and least hazard for toxicity Other antibiotics (notably penicillin aureomycin and chloramphenicol) have supplementary value against secondary invaders none being intrinsically tuberculocidal to a significant degree Under investigational scrutiny and not commercially available are benzothiazole fumigacin galacturonide lupulin subtilin and vole vaccine In the group of obsolete preparations are gold and the tuberculins

6 Included in the accompanying chart are also anti allergens Obviously tuberculocides are of no benefit in the treatment of allergic *hypersensitivity manifestations*

For prevention and treatment of histamine type responses various antihistamines are recommended (p 4212) for control of exudative and proliferative reactions due to perversions of bodily defenses cortisone and ACTH should prove as specific as in the management of related lesions in rheumatic fever and rheumatoid arthritis Until these products become commercially available the practitioner may tentatively try products that are currently on the market These include artisone (Wyeth) and combined desoxycorticosterone (percorten Ciba) with ascorbic acid

7 The most effective available tuberculostatic and tuberculocidal antibiotics are streptomycin and its near relatives dihydrostreptomycin neomycin and terramycin Unfortunately none of the streptomycins is of sufficient potency to cure tuberculosis At best they appear capable of holding off invasion until the natural forces of resistance are capable of conquering the invading microbe Unfortunately also more than any other antibiotic with the possible exception of sulfonamides the streptomycins are capable of inducing antitherapeutic reactions (p 4133) tubercle bacilli rapidly develop bacterial immunity as manifested by the phenomenon of fastness prolonged administration of reasonably large doses produces appreciable neurovestibular toxicity and finally host tissues may develop *hypersensitivity manifestations* to the therapeutic product itself

SPECIFIC PREPARATIONS ADVOCATED FOR PREVENTION AND TREATMENT OF TUBERCULOSIS

ACTH

For control of proliferative and exudative allergic hypersensitivity manifesta tions as particularly illustrated by tuberculids (p 4169) Not commercially available See Cortisone

Adrenal Cortical Extracts

See Cortisone

Antihistamines

For prevention and treatment of histamine type allergic hypersensitivity mani festations wh ther due to protein of tubercle bacillus or to complex formed by union of ho t protein and tuberculocidal anti infective agent, particularly streptomycin Routine administration advocated during activity due to bac terial invasion and during and following therapy with tuberculocides

Ascorbic acid

See Cortisone

Aureomycin N N R

Po ent anti infective agent not tuberculocidal but effective in eradicating secondary invader thus supplementing and fortifying tuberculocides

BCG

Bacillus Calmette-Guerin for vaccination of tuberculin negative reactors under circumstances elsewhere detailed (p 4602) No official or commercially available preparation

Benzothiazole

Synthetic antibiotic currently being investigated in experimental tuberculosis Not commercially available

Calciferol

A preparation of vitamin D_2 used pr marily in the treatment of cutaneous tuber culosis (p 4322)

Carbamyl

Under investigation Not commercially available

Chloramphenicol N N R

Potent anti infective agent not tuberculocidal but eff ctive in eradicating secondary invaders thus supplementing and fortifying tuberculocides

Conteben (TB I 698)

See thiosemicarbazones A synthetic tuberculocide with the formula 4 amino acetyl benzaldehyde thiosemicarbazone In dos s of 2 mg /Kg /day exhibits efficacy approximating that of PAS

Cortisone (Cortone)

For control of proliferative and exudative allergic hyper ensitivity manifesta tions as particularly illustrated by tuberculids (p 4169) Until commercially available try desoxycorticosterone (percorten Ciba) and a corbic acid.

Desoxycorticosterone

See Cortisone

SPECIFIC PREPARATIONS ADVOCATED FOR PREVENTION AND TREATMENT OF TUBERCULOSIS (*Continued*)

Dihydrostreptomycin

Resembles streptomycin in tuberculocidal potential and in therapeutic hazard. Because neurotoxicity does not become apparent until some time after cessation of drug prefer streptomycin whose administration may be discontinued at onset of untoward manifestations All in all investigators are dubious of the usefulness of dihydrostreptomycin.

Gold

Obsolete in treatment of tuberculosis (p 4346)

Lupulin

Antibiotic derived from hops Under investigation for treatment of tuberculosis Not commercially available

Neomycin

In doses of 3 mg/Kg/day approximates tuberculocidal activity of streptomycin with somewhat less toxicity Not yet commercially available

New Tuberculin N N R

Bacterial emulsion of which 1 cc corresponds to 5 mg of tubercle bacilli Not commercially available For prophylactic use prefer BCG

New Tuberculin TR N N R

Each cc contains residue of 10 mg of living dried tubercle bacilli Not commercially available For prophylactic vaccination prefer BCG

New Tuberculin BE Dried N N R

Tubercle bacilli dried and ground mixed with a suitable base and made into tablets adjusted so that each represents the desired amount of New Tuberculin BE per cc Not commercially available For prophylactic vaccination prefer BCG

New Tuberculin TR Dried N N R

As New Tuberculin above but disintegrated dried and made into tablets Not commercially available For prophylactic vaccination prefer BCG

Old Tuberculin U S P

For skin testing Use Lederle Lilly or Parke Davis products for Mantoux (pp 263 561) use Parke Davis Old Tuberculin for Von Pirquet For Vollmer patch test use Lederle Tuberculin Patch Test each strip having two test squares and one control square (Fig 35 p 264 and Fig 34 p 263)

Para-aminosalicylic Acid (PAS)

Tuberculocidal synthetic for use alone in the treatment of tuberculosis or concurrently with streptomycin Commercially available in powder form (Merck) or in tablets of 0 3 gm (Parke Davis) Recommended daily dose 10 to 12 gm See below

Penicillin N.N R

Potent anti infective agent not tuberculocidal but effective in eradicating secondary invaders thus supplementing and fortifying tuberculocide

Percorten

See Cortisone

SPECIFIC PREPARATIONS ADVOCATED FOR PREVENTION AND TREATMENT OF TUBERCULOSIS (*Continued*)

Purified Protein Derivative (PPD) U S P

For Mantoux intracutaneous test Tablets of first strength equal 0 00002 mg second strength 0 005 mg (Parke Davis)

Streptomycin N N R.

Currently the mo t ucce sful tuberculostatic and tuberculocidal antibiotic See below

Subtilin

Antibiotic under experimental investigation Not commercially available

Sulfones

Promizole promin diasone and sulphetrone as u ed in the treatment of leprosy (p 4386) Too toxic for use in tuberculosis except as desperation sup plementation in overwhelming infection uch as tuberculous meningitis or miliary forms of tuberculosis

T Acetamidobenzaldehyde

A thiosemicarba one commercially available as conteben

TB I 698

A thiosemicarbazone commercially available as conteben and tibione

Thiosemicarbazones

Synthetic chemotherapeutic agents with tuberculocidal potential Pre ently available in Europe as Conteben or TB I 698 Marketed in tablets containing 0 125 gm with an equal quantity of sulfathiazole Given orally in doses of 2 mg /Kg /day Conteben or TB I (Tibione) exhibits efficacy approximating that of PAS but with greater toxic potential See below

Tibione (Schenley)

Commercially available in 25 and 50 mg tablets in U S A.

Tuberculin Denys N N R

A glycerin broth culture of tubercle bacilli Not commercially available For prophylactic vaccination prefer BCG

Vitamin D

See calciferol

Vole Vaccine

Prepared from vole bacilli killed by ultraviolet rays Used experimentally to produce immunity against M tuberculos s in guinea pigs Not commercially available but regarded as affording protection equal to BCG in experimental animals

8 With remarkable ingenuity investigators have sought to over come objections to streptomycin therapy of tuberculosis Concurrent administration of para aminosalicylic acid appears to reduce emergence of fast strains from an expected 80 per cent to 30 per cent concurrent prescription of antihistamines reduces neurovestibular toxicity and lessens histamine type allergic hypersensitivity manifestations such as toxicoderms drug fever leukocytosis and eosinophilia

9 All experienced clinicians are opposed to routine use of streptomycin in tuberculosis In general indications for streptomycin therapy include fulminating infections such as miliary or meningeal tuberculosis in which the life of the patient hangs in the balance exudative pulmonary lesions persistence of tubercle bacilli in secretions or excretions tension cavities even without demonstrable organisms in the sputum and failure to respond or actual progression, despite nonspecific therapy with or without surgical intervention after a scrupulous trial period of 3–4 months

10 During streptomycin therapy the following information must be collected

(a) daily weight
(b) rectal temperature record
(c) biweekly urine analysis
(d) weekly blood count
(e) determination of blood urea and non protein nitrogen every second week
(f) audiometer readings at fortnightly intervals daily determination of detection of whispered voice
(g) chest radiography pretreatment and at monthly intervals thereafter
(h) estimation of erythrocyte sedimentation rate once a month
(i) examinations of sputum gastric contents stool urine or sections of tissue pretreatment and monthly thereafter
(j) guinea pig inoculations at monthly intervals after direct and concentrated specimens have been reported negative
(k) determination of organism sensitivity to streptomycin at monthly intervals
(l) protection of streptomycin handlers by use of gloves and a mask while making solutions and giving injections Only in this way is it possible to minimize contact dermatitis or cheilitis in personnel

11 The toxicology of streptomycins has received previous consideration (p 105) In the presence of an exfoliative dermatitis stop antibiotic and substitute dihydrostreptomycin with bone marrow depression discontinue antibiotic permanently with diminution in hearing temporarily interrupt streptomycin injections and resume only if hazard of the tuberculosis exceeds hazard of permanent deafness with albuminuria and casts in the urine exercise caution particularly in patients with evidences of depressed renal function or with renal tuberculosis with nitrogen retention stop antibiotic unless threat of infectious process is grave at onset of vertigo reduce amount of drug and consider cessation at least temporarily if clinical circumstances permit briefly interrupt antibiotic therapy in the presence of drug fever nausea vomiting circumoral paresthesia or toxicoderms suggestive of histamine type allergic hypersensitivity with demonstrable increased bacterial resistance supplement with para aminosalicylic acid or if PAS is already on the therapeutic program increase daily dose to 15 gm. if possible

12 In acute emergencies such as meningeal and acute miliary tuberculosis and in exudative pulmonary infections give drug toxicity only secondary consideration Under these circumstances inject intra muscularly 1 gm of streptomycin once twice or thrice daily for 120 days provided that menacing toxic manifestations do not appear Many authorities favor simultaneous intrathecal instillations in meningeal forms of 0 05 gm of streptomycin every second or third day for approxi mately one month However we are among those who frown on intra thecal therapy of any type (p 4409)

13 With less urgent indications for streptomycin therapy experts agree that smaller doses are preferable to larger amounts Currently it is the opinion that an optimum course consists of daily do es of 1 gm for forty two days (Council on Streptomycin Therapy of the Veterans Administration) In the experience of most phthisiologists the 6 week period of streptomycin therapy affords maximum therapeutic efficacy and minimum chances for toxicity or emergence of fast bacterial strains

14 There appears to be fairly unanimous agreement that 90 day courses are required in more resistant forms of extrapulmonary tuber culosis such as involvements of tracheobronchial tree larynx lymph nodes bone cartilage joints mouth pharynx intestines peritoneum pericardium skin ocular structures and ears

15 Exercise particular precautions in genito urinary tuberculosis since diminution of renal function may increase blood levels of strep- tomycin four fold and result in toxic manifestations from seemingly insignificant doses Before treatment is instituted and weekly there after estimations of renal function and blood chemistry are required With impairment of kidneys interrupted cour es merit consideration antibiotic may be given three days on and three days off or fifteen days on and fifteen days off preferably with concurrent para aminosalicylic acid

16 As an adjuvant to surgery streptomycin therapy is particularly useful especially if used in conjunction with para aminosalicylic acid Before performance of most operative procedures a 1 week course of treatment is highly recommended following operation antibiotic is injected for at least two to three weeks

17 There are almost as many variants in streptomycin therapy as there are investigators Certain physicians recommend that the daily dose be a single injection of 1 gm others deposit 0 5 gm twice daily still others continue therapy for ninety to one hundred twenty days in the obsence of toxic manifestations

18 Interrupted schedules are favored by some experienced clini cians Pecommended routines call for antibiotic two days on and one day off three days on and three days off fifteen days on and fifteen days off and finally 1 gm twice weekly for 35 injections (120 days)

19 Para aminosalicylic acid (PAS) currently is second choice to streptomycin as a tuberculocide Doses of 3 gm four times daily to total 12 gm per 24 hours are recommended

20 Given alone para aminosalicylic acid has definitive but only

moderate tuberculostatic and tuberculocidal properties In favorable responses temperature approaches normal sedimentation rate is decreased cough is diminished expectoration is reduced bacilli diminish in numbers or disappear from sputum appetite improves body weight increases and blood count rises

21 Other than gastro intestinal disturbances which disappear on interruption of therapy para aminosalicylic acid appears to have no significant toxicity Compared to thiosemicarbazones *PAS* is equally tuberculocidal but considerably less toxic

22 *With gastro intestinal distress arising from* PAS discontinue drug temporarily and resume as soon as stomach is tolerant Begin retreat ment with 6 gm daily increase gradually to full therapeutic dose if possible if less than 6 gm daily are tolerated discontinue drug since no appreciable tuberculocidal effect can be anticipated from low con centrations

23 In addition to its inherent use as a tuberculocide para amino *salicylic acid functions synergistically with streptomycin* Combinations of the two tuberculocides appear to be more effective than the sum of both drugs used separately In addition PAS permits use of smaller doses of streptomycin and thus reduces the hazard of drug toxicity it discourages the emergence of streptomycin resistant organisms and *additionally is as tuberculocidal in its effect on streptomycin resistant* tubercle bacilli as it is on streptomycin sensitive strains

24 The most recent additions to the tuberculocides are the thiosemi carbazones (8th Streptomycin Conference Atlanta Georgia Nov 12 1949) Commercially available is conteben in Germany referred to also in the literature as TB I Tibione and TB I 698 The recommended oral dose is 2 mg per kg of body weight per day or 140 mg for the *average adult weighing 150 lbs Tibione is now commercially available* in the United States Tablets of 25 and 50 mg are supplied by Schenley

25 The thiosemicarbazones are tuberculocidal in the test tube and in clinical experimentation They are less efficacious than streptomycin but about of equal potency with PAS Unfortunately they are con siderably more toxic than either *previously mentioned preparation* They may produce gastric irritation nausea vomiting hepatitis irrita bility headache increased intracranial pressure conjunctivitis derma toses hemolysis agranulocytosis aplastic anemia and toxic neuritis On the favorable side encouraging results of thiosemicarbazone therapy have been noted in exudative pulmonary lesions and in *intestinal* laryngeal and osteo arthritic forms of tuberculosis The new drug however is useless in the management of miliary and meningeal infec tions Prolonged drug administration is desirable the average recom mendation being no less than 6 months and preferably a year

26 Because of encouraging results of sulfone therapy in *leprosy* concurrent administration of promizole with streptomycin has been recommended in the treatment of tuberculous meningitis However the Council on Streptomycin Therapy of the Veterans Administration found no objective evidences of the superiority of the combination of sulfone and streptomycin over streptomycin alone and *joint use of the*

two drugs was distinctly more troublesome Nevertheless in serious exigencies such as meningeal and acute miliary tuberculosis promizole may be tried as fourth choice to streptomycin PAS and thio emicarba zone in doses of 2 gm four times daily to achieve blood levels of 2 to 3 mg per 100 cc Toxic manifestations of sulfone therapy are elsewhere detailed (p 4552)

27 Preceding concurrently and following streptomycin therapy administer antihistamines as pyribenzamine benadryl or one of their substitutes in daily doses of 200 to 400 mg The antihistamines have negligible toxicity and may prevent or alleviate histamine type allergic hypersensitivity manifestations whether due to tuberculo protein or to administration of antibiotic agent

28 In the presence of secondarily infected tuberculous le ions favor combined antibiotic therapy in order to eliminate streptomycin resistant organisms As first choice give deposits of procaine penicillin G in aqueous suspension in daily do es of 300 000 to 600 000 units Peni cillin has negligible digestive side effects whereas aureomycin and chloramphenicol may produce nausea and vomiting interfering with use of tuberculocides particularly para aminosalicylic acid and thio emicarbazones

29 A complete therapeutic schedule where indications exist may call for daily intramuscular injections of 1 gm of streptomycin and of 300 000 to 600 000 units of procaine penicillin G in aqueous suspen sion and of oral doses of 200 to 400 mg of antihi tamine with 12 gm of para amino alicylic acid or 50 to 200 mg of thiosemicarbazone

30 Despite the complexity of the pharmacologic schedule the sea soned practitioner will not neglect mechanical procedures particu larly collapse therapy As soon as the therapeutic schedule has been inaugurated consult with phthisiologist and thoracic surgeon for a discussion of pneumoperitoneum pneumothorax or phrenic paralysis or of operative procedures previously outlined

Practical Management

Arrangement of a therapeutic program for the individual tubercu lous patient poses a formidable challenge to the practitioner Obvi ously no single static schedule can meet variables due to bacillary invasion host tissue reactions and observed response to prescribed therapeutic products and procedures The discussions of practical management which follow are relatively fluid recommendations in which prime emphasis is placed on only three of the many variables i e tuberculin reactivity the presence or absence of demonstrable organic lesions and evidences of activity

I TUBERCULIN TEST NEGATIVE NO DEMONSTRABLE LESIONS NO CLINICAL EVIDENCES OF ACTIVITY

1 An increasing number of children and many adults dwelling under optimum conditions of civilization reveal tuberculin negativity It must be assumed that these patients are virginal and that their

moderate tuberculostatic and tuberculocidal properties In favorable *responses temperature approaches normal sedimentation rate is* decreased cough is diminished expectoration is reduced bacilli diminish in numbers or disappear from sputum appetite improves body weight increases and blood count rises

21 Other than gastro intestinal disturbances which disappear on interruption of therapy para aminosalicylic acid appears to have no significant toxicity Compared to thiosemicarbazones PAS is equally tuberculocidal but considerably less toxic

22 With gastro intestinal distress arising from PAS discontinue drug temporarily and resume as soon as stomach is tolerant Begin retreatment with 6 gm daily Increase gradually to full therapeutic dose if possible if less than 6 gm daily are tolerated discontinue drug since no appreciable tuberculocidal effect can be anticipated from low concentrations

23 In addition to its inherent use as a tuberculocide para-amino salicylic acid functions synergistically with streptomycin Combinations of the two tuberculocides appear to be more effective than the sum of both drugs used separately In addition PAS permits use of smaller doses of streptomycin and thus reduces the hazard of drug toxicity it discourages the emergence of streptomycin resistant organisms and additionally is as tuberculocidal in its effect on streptomycin resistant tubercle bacilli as it is on streptomycin sensitive strains

24 The most recent additions to the tuberculocides are the thiosemicarbazones (8th Streptomycin Conference Atlanta Georgia Nov 12 1949) Commercially available is conteben in Germany referred to also in the literature as TB I Tibione and TB I 698 The recommended oral dose is 2 mg per kg of body weight per day or 140 mg for the average adult weighing 150 lbs Tibione is now commercially available in the United States Tablets of 25 and 50 mg are supplied by Schenley

25 The thiosemicarbazones are tuberculocidal in the test tube and in clinical experimentation They are less efficacious than streptomycin but about of equal potency with PAS Unfortunately they are considerably more toxic than either previously mentioned preparation They may produce gastric irritation nausea vomiting hepatitis irritability headache increased intracranial pressure conjunctivitis dermatoses hemolysis agranulocytosis aplastic anemia and toxic neuritis *On the favorable side encouraging results of thiosemicarbazone* therapy have been noted in exudative pulmonary lesions and in intestinal laryngeal and osteo arthritic forms of tuberculosis The new drug however is useless in the management of miliary and meningeal infections Prolonged drug administration is desirable the average recommendation being no less than 6 months and preferably a year

26 Because of encouraging results of sulfone therapy in leprosy concurrent administration of promizole with streptomycin has been recommended in the treatment of tuberculous meningitis However the Council on Streptomycin Therapy of the Veterans Administration found no objective evidences of the superiority of the combination of sulfone and streptomycin over streptomycin alone and joint use of the

III TUBERCULIN TEST POSITIVE DEMONSTRABLE LESIONS BY PHYSICAL EXAMINATION OR RADIOGRAPHY NO EVIDENCES OF ACTIVITY

1 Assume that these patients have suffered subclinical infection or ancient invasion with development of active immunity and recovery through fibrosis and cicatrization with or without calcification

2 Treat by skillful neglect Other forms of specific therapy are distinctly contraindicated

3 In the presence of future evidences of active invasion with fever tachycardia and a rapid sedimentation rate differentiate between exacerbation of the ancient tuberculous process and development of intercurrent infection

4 Exclude tuberculosis by absence of demonstrable acid fast bacilli by demonstration of another microbic invader by therapeutic response to non tuberculocidal antibiotic agents such as penicillin aureomycin or chloramphenicol or by spontaneous subsidence of the infectious process within the course of a few days or weeks

5 In convalescence from intercurrent infection watch carefully for evidences of recrudescence of the tuberculous infection Insist on a long period of convale cence Forbid resumption of activities until temperature pulse rate sedimentation rate chest radiographs and clinical manife tations leave no doubt as to the completeness of recovery

IV TUBERCULIN TEST POSITIVE MINIMAL LESIONS OF PRIMARY INFECT WITHOUT EXUDATION OR DESTRUCTION EVIDENCES OF SUBCLINICAL TO MILD ACTIVITY

1 Request a round table consultation with phthisiologist and thor acic surgeon Fully discuss all aspects of therapy including use of tuberculocidal drugs and supplementary mechanical measures of col lapse accomplished by pneumoperitoneum pneumothorax phrenic nerve crushing or avulsion

2 Institute non specific treatment for tuberculosis (pp 267–272) Consider home versus sanitarium therapy

3 Order daily doses of 200 to 400 mg of pyribenzamine benadryl or a substitute antihistamine to minimize or prevent histamine type hypersensitivity reactions

4 Prescribe 3 gm of para aminosalicylic acid four times daily for tuberculocidal effects without hazard of significant toxicity

5 Explain to patient and family reasoning behind reservation of streptomycin therapy

6 Emphasize favorable aspects of prognosis as a measure of psychotherapy

Continuing Care (Favorable Course)

1 Insist on a prolonged period of convale cence Try to prevent resumption of normal activity until the expiration of six to twelve months

defenses have never been tested by the tubercle bacillus Depending on many external circumstances the patient may be exposed to compulsory mass or individual vaccination or he may be treated by skillful neglect

2 Compulsory BCG vaccination of tuberculin non reactors is practiced in Sweden Norway and Denmark

3 Mass BCG vaccination is advocated in areas where there is a high tuberculosis morbidity and mortality in the presence of bad housing malnutrition and exposure to inclement weather and in over crowded institutions such as barracks asylums homes and jails (p 4602) The United Nations have vaccinated 5 400 000 children in Europe and in Morocco Tunisia Algiers Egypt Israel Lebanon China India Pakistan Ceylon etc In the United States mass vaccination is currently practiced among American Indians and in certain underprivileged areas in the deep South

4 Individual BCG vaccination is recommended for personal reasons such as heavy exposure to open tuberculosis in the home infants children and marital partners of the tuberculous occupational contact as in the case of physicians nurses medical students laboratory technicians and the personnel of sanitaria or hospitals which admit patients with tuberculosis lowered resistance due to malnutrition contact with masses of tuberculous patients as occurs when occupation troops police and other authorities are assigned to duty in devastated areas

5 The general practitioner unfamiliar with the technics of BCG vaccination may request that the procedure be done by a public health authority or a consultant

6 For the first month following vaccination protect patients from exposure to tuberculosis Infants of tuberculous mothers especially must be segregated until a natural active immunity is built up

7 For the present regard vaccination with vole bacillus as purely experimental and chemoprophylaxis with antibiotics and tuberculocides as impracticable

II TUBERCULIN TEST POSITIVE NO DEMONSTRABLE LESIONS NO EVIDENCES OF ACTIVITY

1 Tuberculin positive reactors who display no evidences of tuberculous lesions or of activity may be regarded as having developed an immunity mechanism after exposure to the organism

2 Tuberculin negative reactors inoculated with BCG vaccine develop tuberculin positivity within the course of the month On the basis of extensive experiences it may now be stated that artificial immunity created by the avirulent tubercle vaccine strikingly reduces morbidity and mortality

3 Whether tuberculin positivity has been achieved by natural or artificial means consider the patient adequately protected Treat by skillful neglect Other measures are meddlesome and distinctly contraindicated

7 If pneumothorax cannot be accomplished for technical rea ons consider pneumoperitoneum crushing or avulsion of the phrenic nerve intrapleural pneumolysis thoracoplasty or excision of the grossly infected end organ such as kidney testicle epididymis tube ovary or lymph node

Continuing Care (Favorable Course)

1 At the termination of forty two days of streptomycin therapy review status of patient with phthisiologist and thoracic surgeon

2 *Do not make the mistake of prematurely discontinuing a success* ful therapeutic schedule In the absence of toxic manifestations from streptomycin favor continuance of antibiotic therapy particularly in the presence of lesions of trachea bronchi larynx lymph nodes bones joints cartilage mouth pharynx intestines peritoneum pericardium skin ocular structures or ears

3 In the presence of mild toxic manifestations taper off tuberculo cides Try injections of streptomycin for three days on and three days off alternating with oral doses of para aminosalicylic acid try periods of fifteen days of treatment with intervening treatment holidays of fifteen days or inject streptomycin in doses of 1 gm twice weekly for 4 months omitting para aminosalicylic acid on injection days

Continuing Care (Unfavorable Course)

1 In the presence of bacterial fastnes discontinue streptomycin increase dose of para aminosalicylic acid to 15 gm daily or substitute dihydrostreptomycin neomycin or terramycin for the original tuber culocide

2 Cautiously try to increa e the dose of the substituted streptomycin using perhaps 1 5 to 2 gm daily

3 If the patient is intolerant of para aminosalicylic acid substitute tibione or any other commercially available thiosemicarbazone Start with a daily dose of 50 mg and increa e to 200 mg unless toxic symptoms are encountered (p 4609)

4 Renew consultations with thoracic surgeon Consider more exten ive surgical procedures as measures of desperation

VI TUBERCULIN TEST NEGATIVE OR POSITIVE FULMINATING EXUDATIVE LESIONS OR MANIFESTATIONS OF SYSTEMIC HEMATOGENOUS OR LYMPHOGENOUS DISSEMINATION MENACING EVIDENCES OF ACTIVITY WITH URGENT JEOPARDY TO LIFE

1 Insist on hospitalization and inauguration of measures previously advocated for less serious infections institute non specific measures of general hygienic therapy (pp 267–272) prescribe oral doses of anti histamines and of para aminosalicylic acid and try to eradicate sec ondary infection with intramuscular deposits of procaine penicillin or oral use of aureomycin or chloramphenicol

2 Insist on record of rectal temperature at least two full days in each week

3 Schedule monthly visits for chest radiography and estimation of erythrocyte sedimentation rate

Continuing Care (Unfavorable Course)

1 With continued pyrexia tachycardia failure to gain weight and strength persistence of lesions and/or bacilli in sputum resort to schedule suggested for those in category V next outlined

2 The complication of hemoptysis is usually more alarming than menacing Unless there has been a massive or continued loss of blood it is only necessary to reassure and sedate the patient Massive hemoptysis however calls for heroic measures the best available hemostatic procedure being induction of artificial pneumothorax or collapse of the lung by open surgical procedure meanwhile compensating for blood loss by transfusion

V TUBERCULIN TEST POSITIVE PERSISTENT OR PROGRESSIVE LESIONS WITH EVIDENCES OF EXUDATION AND TISSUE DESTRUCTION SIGNS OF MODERATE ACTIVITY

1 Institute or continue suggestions for management of infections of lesser severity Insist on round table consultation with phthisiologist and thoracic surgeon Inaugurate non specific treatment for tuberculosis (pp 267–272) order antihistamine and prescribe para amino-salicylic acid

2 Start intramuscular injections of streptomycin Deposit 0 5 gm twice daily or 1 gm daily for a probatory period of forty two days

3 At each daily visit note temperature records weight acuity of hearing and complaints of vertigo or digestive disturbances possibly due to drug

4 Order urine examinations twice weekly blood counts once weekly blood chemistry each fortnight chest radiography and examination of sputum gastric contents stool urine or tissue sections at monthly intervals Request bacteriologist to determine organism sensitivity to streptomycin at each examination

5 In the presence of suspected secondary bacterial invasion by organisms possibly resistant to streptomycin consider combined antibiotic therapy For maximum coverage of the bacterial spectrum give chloramphenicol orally using approximately 50 mg per kilogram per day (3 5 gm for the average adult weighing 150 lbs) For less complete coverage and less hazard of gastric intolerance deposit intramuscularly 300 000 to 600 000 units of crystalline procaine penicillin G in aqueous solution once daily

6 Favor induction of pneumothorax if the lesion is predominantly unilateral if there are greater evidences of tissue destruction or exudation in one lung as opposed to the other or if the response to combined tuberculocides and antibiotics is not satisfactory within the course of the first two weeks

the home or in industry until a significant active immunity has been developed

2 In fulminating infections such as miliary tuberculosis and tuber culous meningitis when the skin test is negative de pite an active invasion with acid fast organisms more intensive tuberculocidal therapy is required since the patient has no resources with which to fortify artificial chemotherapeutic procedures

3 In certain rare low grade tuberculous manifestations such as arcoidosis (p 3271 Fig 954 p 3263) it must be assumed that the patient is in a state of anergy and hence incapable of producing anti body Under these circumstances consider artificial stimulation of antibody by use of tuberculins and by administration of vitamin D_2 or dihydrotachysterol (p 4322)

TULAREMIA

[Deer Fly Fever Rabbit Fever]

Principles of Diagnosis and Therapy

1 Experiences in Arkansas suggest that tularemia (p 323) is more often tick borne than transmitted by handling of infected animals (rab bits squirrels etc)

2 Treatment has been revolutionized first by the specificity of streptomycin later by aureomycin and chloramphenicol

Practical Management

Immediate Care

1 Irrespective of type (pp 323–324) arrange for ho pitalization if possible

2 Institute non specific treatment for generalized infections (pp 68–73)

3 Notify public health officials

4 Order a priming dose of 100 mg per kilogram of body weight (7 gm for average adult weighing 150 lbs) of aureomycin or chlor amphenicol Order 4 products (1 gm) every few minutes until total dose of 28 has been ingested With each dose give milk soup cream cheese or ice cream

5 For ophthalmic infections instill aureomycin ophthalmic solution (1 cc = 25 mg) into conjunctival sac

6 Use moist wet applications to local lesions and lymph nodes Avoid incision (Fig 47 p 319)

Continuing Care (Favorable Course)

1 Continue antibiotic using 4 products (1 gm) every three hours except at 3 A M until patient has been afebrile for at least forty

2 After consultation with phthisiologist and thoracic surgeon increase streptomycin dosage to 1 gm thrice daily

3 Try to increase daily dose of para aminosalicylic acid to 15 gm If stomach is intolerant substitute thiosemicarbazone in daily doses of 50 to 200 mg

4 In tuberculous meningitis consider intrathecal injections of 0 05 gm of streptomycin Although this procedure appears illogical and hazardous it is recommended by many experienced clinicians (p 4409)

5 In the presence of a negative response to streptomycin or of emergence of fast bacterial strains substitute dihydrostreptomycin neomycin or terramycin

6 With failure of response and gastric intolerance to para amino salicylic acid and thiosemicarbazone cautiously substitute promizole in doses of 2 gm four times daily carefully observing urine and blood count

VII TUBERCULIN TEST POSITIVE DEMONSTRABLE ALLERGIC HYPERSENSITIVITY REACTIONS (TUBERCULIDS) NEGLIGIBLE EVIDENCES OF ACTIVITY

1 Regard lesion as an allergic *manifestation* rather than a bacteria invasion

2 Prescribe antihistamine in daily oral doses up to 800 mg of pyribenzamine or benadryl

3 Treat exudative and proliferative lesions with cortisone or ACTH when available In the meantime try probatory therapy with artiscre injected intramuscularly or with the combination of desoxycorticosterone and ascorbic acid To accomplish the latter objective deposit intramuscularly 1 cc of percorten (Ciba) containing 5 mg of desoxy corticosterone Follow in 5 minutes by intravenous injection of 10 cc of 10% ascorbic acid Continue treatments daily for three days Unless response is spectacular abandon therapy at the end of this trial period

4 For lesions of lupus vulgaris or scrofuloderma prescribe vitamin D Give 50 000 units of calciferol in oil thrice daily Follow a similar schedule in lupus miliaris disseminatus faciei rosacea like eruption of Lewandowski erythema induratum cutaneous and generalized sarcoidosis and other possible tuberculids

5 Omit use of tuberculocides Streptomycin particularly may give rise to similar allergic hypersensitivity manifestations and can do no good

6 With persistence of lesions consult dermatologist Discuss radio therapy

VIII TUBERCULIN TEST NEGATIVE DEMONSTRABLE INVASIVE LESIONS EVIDENCES OF ACTIVITY

1 The tuberculin test does not become positive for at least one month after BCG vaccination Under these circumstances segregate infants of tuberculous mothers and others exposed to tuberculosis in

or 7 gm for average adult weighing 150 pounds) Give 2 products every few minutes until total number of 28 has been ingested

Continuing Care (Favorable Course)

1 Maintain antibiotic levels with total daily dose equal to priming dose i e 4 products (1 gm) every 3 hours except at 3 A M

2 Warn patient not to expect specific clinical improvement for forty eight hours

3 Reduce daily dose after two weeks to 6 gm after three weeks to 4 gm but continue for another three to six weeks to prevent relapse or recurrence

Continuing Care (Unfavorable Course)

1 Since complications may occur despite deferve cence these must be dealt with as in the earlier period before specific therapy was suc ce sfully instituted (p 234)

2 For relapse increase drug dosage to original level or if necessary to double or treble quantities

3 For hemorrhage set up an intravenous drip and infuse plasma until cross matched blood can be obtained Do not hesitate to intro duce 1000 to 1500 cc if bleeding is massive and continued

4 For perforation consider surgery under local anesthesia

5 If stomach is intolerant give chloramphenicol by duodenal tube improvising a suspension in milk or oup

TYPHUS FEVER

[Kenya Tick Fever Manchurian Fever Queensland Coastal Fever South African Tick Fever Toulon Ship Fever Torbadillo Shop Typhus of Malaya]

General Principles of Diagnosis and Therapy

1 For present purposes louse borne and rat or flea borne typhus fever may be regarded as one and the same disease (p 369)

2 Aside from a history of the presence of the disease the diagnostic feature is the characteristic rash (Fig 57 p 370)

3 In the laboratory the diagnosis is e tablished by Weil Felix reac tion (p 372) and by inoculation of guinea pigs (Fig 12A p 63)

4 The etiologic Rickettsia prowazeki is insensitive to sulfonamide penicillin and streptomycin but sensitive to para aminobenzoic acid and especially to aureomycin and chloramphenicol

Practical Management

Prophylaxis

1 Active immunity is accomplished by 3 subcutaneous injections each of 1 cc of Parke Davis typhus vaccine (p 4209) Immunity per

eight hours Give 1 gm every six hours for another forty eight hours and then discontinue if all is well

Continuing Care (Unfavorable Course)

1 If stomach is tolerant double dose of chosen antibiotic or continue above dose and give an equal amount of the alternate

2 If stomach is intolerant to either antibiotic use alternate in similar doses or substitute terramycin

3 If patient is intolerant of both aureomycin and chloramphenicol substitute streptomycin Inject intramuscularly 1 gm as priming dose Maintain level with 0 5 gm every eight or twelve hours depending on response Continue for three or four days after defervescence

4 With first dose of streptomycin start oral antihistamine prophylactically Give 200 mg daily of pyribenzamine or benadryl (p 4212) Continue for two weeks after last dose

5 Obsolete are human convalescent tularemia antiserum and heterologous tularemia antibacterial serum

6 Tularensis vaccine never commercially available also is obsolete For prevention rely on chemoprophylaxis (p 4362)

TYPHOID FEVER

Principles of Diagnosis and Therapy

1 Whereas there have been no significant contributions to the diagnostic pathologic and clinical features of typhoid fever (p 225 Fig 25 p 231) specific therapy with chloramphenicol (p 4279) has revolutionized the management of a disease for which previously only supportive and symptomatic management was available (p 236)

Practical Management

Prophylaxis

1 Give routine immunization with typhoid vaccine (p 4209) Triple vaccine containing additionally paratyphoid A and B has wisely been dropped by the Council since it added appreciably to reactions but inappreciably to protection

2 Use insecticides (p 4373) and other methods of fly control to prevent dissemination of microbe by insect vectors

3 Treat human carriers with insoluble sulfonamides (p 4548) streptomycin or chloramphenicol for sterilization of urines and stools Consider cholecystectomy if carrier state fails to respond to non operative therapy

Immediate Care

1 Institute non specific measures previously described (p 236) since complications may occur despite specific therapy

2 Order a priming dose of chloramphenicol (100 mg per kilogram

Tyrozets Throat Lozenges (Sharp & Dohme) containing tyrothricin 1 mg benzocaine 5 mg

Bacteriology

Tyrothricin contains two water oluble crystalline polypeptides Gramicidin the more active is relatively non toxic and is selectively effective against gram positive organisms the ether soluble component tyrocidin is bactericidal against a variety of organi ms but is so toxic to ti sue cells that the antibiotic cannot be given parenterally and its utilization is completely limited to topical application

The combined gramicidin and tyrocidin preparation exhibits anti biotic activity against pneumococci streptococci Co diphtheriae staphylococci anaerobic streptococci beta hemolytic streptococci and anaerobic bacilli

The antibacterial activity of tyrothricin is more rapid than that of penicillin It is unimpaired by the presence of tissue extract or necrotic tissue

Antitherapeutic Devices

While tyrothricin is toxic when given parenterally local adminis tration is without inherent toxicity So far as has been determined bacterial resistance does not develop and hypersensitivities are exceed ingly rare

Therapeutics

Tyrothricin and bacitracin (p 4247) repre ent antibiotic prepara tions of choice for local and topical application Between them they take care of mo t organisms that tend to infect wounds of skin and mucous surfaces They are not particularly active sensitizing antigens and if sensitization does occur it does not preclude use of antibiotics in systemic infections when the need is greater For this rea on they are preferred to sulfonamide penicillin treptomycin and aureomycin ointment or dressings for local and topical application

Toxicity

Introduced parenterally tyrothricin is capable of damage to circu lating blood and kidneys In con equence parenteral administration is strictly contraindicated Intranasal applications may cause anosmia

UNCINARIASIS

[Hookworm Di ease Ancylostomiasis Miner s anemia Tunnel Worker s Anemia Tropical or Egyptian Chlorosis]

Principles of Diagnosis and Therapy

1 Establish diagnosis through identification of ova in stools (Fig 1099 p 3730) If necessary concentrate specimen by zinc sulfate flotation method (p 3731)

sists for only six to eight months so that "booster" doses of 1 cc are required every six months while there is danger of infection

2 Individual prophylaxis also is accomplished by use of insecticides (p 4373) particularly DDT aerosol bombs and by raticides on the premises (p 4374)

Immediate Care

1 If possible remove patient to hospital equipped for care of infectious disease Under any circumstances institute generic care for treatment of the infected patient (pp 68–73)

2 Order a priming dose of 3 to 7 gm of aureomycin or chloramphenicol (approximately 50 to 100 mg per kilo for the average adult weighing 150 lbs)

3 If stomach is intolerant or the patient is comatose or otherwise unable to swallow instill antibiotic transduodenally or rectally or inject intravenously 100 mg of aureomycin hydrochloride and repeat every three hours until the patient is able to ingest medication

Continuing Care (Favorable Course)

1 Maintain antibiotic levels by giving 3 to 4 gm every twenty four hours divided into four equal doses

2 Continue antibiotic treatment until patient has been afebrile for at least three or four days The dose may then be halved for another period of three or four days

Continuing Care (Unfavorable Course)

1 If stomach is intolerant to aureomycin substitute chloramphenicol in the same dosage or terramycin

2 If patient can tolerate neither antibiotic and aureomycin hydrochloride is not available for intravenous use substitute the less effective para aminobenzoic acid Give an initial priming dose of 4 to 8 gm with bicarbonate of soda Continue with maintenance dose of 2 gm at 2 hour intervals day and night until the patient has been afebrile for at least forty eight hours (p 4445)

3 Typhus antirickettsial serum never officially approved or commercially available is obsolete

TYROTHRICIN

Tyrothricin is an antibiotic agent extracted from cultures of B brevis a soil organism

Available Products

Tyrothricin (Parke Davis) 2% solution in 10 cc vials
Tyrothricin Concentrate (Sharp & Dohme) 2 5% solution in 10 and 20 cc vials
Tyroderm (Tyrothricin) Cream (Sharp & Dohme)

of infections Unfortunately there is potential toxicity including nausea vomiting convul ions coma and on occasions fatality

5 Excessively toxic and relatively ineffectual are beta naphthol car bon tetrachloride thymol and santonin

URETHRITIS NON SPECIFIC NON GONOCOCCIC

Principles of Diagnosis and Treatment

1 There is every justification for the practitioner to regard all instances of urethritis as of gonorrheal origin until the contrary is proven (p 4349)

2 Nevertheless in our experience non specific or non gonococcic urethritis is encountered with some frequency in private practice A grave injustice may be done by an attitude which insists that urethral infection implies sexual exposure (p 2336)

3 The etiology of non specific urethritis is presently unknown There is general agreement that it may occur as part of the syndromes pre ently grouped as erythema multiforme exudativum (p 4323) These latter are all probable variants of the same disease entity

4 Non specific non gonococcic urethritis may exist with and with out other manifestations in the nature of cutaneous rashes or other mucosal disturbances (Reiter s syndrome Stevens Johnson disease etc p 4323)

5 When non specific non gonococcic urethritis is encountered the physician s first obligation is to assure the patient of the non venereal nature of the disease Then it is necessary to state that pecific therapy may be quite ineffectual since the etiologic agent whatever it may be does not respond to penicillin sulfonamide or any other preparation to which gram negative Neisseria ordinarily succumb

6 Probatory anti infective therapy may be attempted using strepto mycin in intramuscular injections of 0 5 to 1 gm twice daily for a few days This failing aureomycin and chloramphenicol merit clinical te ting

7 Despite assurance as to the non venereal nature of non specific urethritis request patient to return after six weeks and again after three months for serologic tests for syphilis (p 337)

URINARY ANTISEPTICS

The problem of urinary antisep is has been simplified through intro duction of highly potent antibiotics of negligible toxicity These replace relatively feeble agents many of which were capable of producing serious untoward reactions

2 Look for evidences of extra intestinal complications including ground itch on soles of feet anemia eosinophilia respiratory signs (fox hole cough) and gastro intestinal disturbances (thickening and prominence of the mucous membranes of duodenum jejunum and ileum producing various digestive disorders)

Practical Management

Prophylaxis

1 Avoid penetration of eggs through soles of feet by use of shoes at all times

2 Insist on hand washing after urination and evacuation and again before ingestion of food

Immediate Care

1 If there is associated ascariasis (p 4240) use preliminary hexylresorcinol *Give 1 gm in hard gelatin capsules while fasting Avoid food for four hours Then purge with 30 to 45 gm sodium sulfate in at least 1 pint of water*

This will prove effectual against ascarias s and will relieve patient of 50 to 60% of Necator and 20 to 30% of Ancylostoma

2 If patient does not suffer simultaneously from ascariasis use tetrachlorethylene as preparation of choice While most observers insist on a period of preparation in which alcohol cream butter and fat are avoided the United States Public Health Service does not believe that this preliminary diet is necessary nor is preliminary purgation insisted upon Order 3 to 4 cc of tetrachlorethylene in hard gelatin capsules After two to three hours follow with 30 to 45 gm sodium sulfate in at least a pint of water Tetrachlorethylene is successful in ridding stools of Necator in 80 per cent of instances but there are only 25 per cent of successes with Ancylostomas

Continuing Care (Unfavorable Course)

1 Hexylresorcinol may be repeated twice at weekly intervals if necessary

2 Provided that it does not cause undue exhilaration or depression tetrachlorethylene may be repeated once at an interval of seven days if necessary

3 Irrespective of anthelmintic used hematinics or transfusions are required if erythrocytes fall below 3 5 million or the hemoglobin reads less than 10 gm

4 With persistence of symptoms and failure of hexylresorcinol and tetrachlorethylene oil of chenopodium merits trial The patient is prepared as for tetrachlorethylene therapy The next morning on a fasting stomach 0 5 cc of oil of chenopodium is administered orally in hard gelatin capsules The dose is repeated at half hour intervals for three doses to total 1 5 cc After two or three hours a saline purge is administered Chenopodium therapy is effectual in 70 to 90 per cent

URINARY ANTISEPTICS (*Continued*)

NU 445

See gantrisin.

Penicillin N N R

Effective only against gram negative and gram po itive cocci Not effective against usual gram negative bacillary invaders Prefer aureomycin chloram phenicol streptomycin ulfonamide and salts of mandelic acid.

Pyridium
(Merck)

Feeble urinary antiseptic with slight analgesic effect on urogenital mucosa Chemically phenyla o-diamino pyridine hydrochloride Commercially avail able as pyridium tablets 0 1 gm Not comparable to aureomycin chloram phenicol sulfonamide streptomycin or salts of mandelic acid

Serenium
(Squibb)

An organic azo dye available in chocolate coated tablets of 1 gm Serenium is a mild urinary antiseptic which colors the urine red It is non toxic and non irritant and is equally effective in acid and alkaline urines However it does not compare in efficacy with aureomycin chloramphenicol sulfonamide streptomycin or alt of mandelic ac d

Sulfonamide

Soluble sulfonamides effective against gram negative bacillary invaders More toxic than aureomycin chloramphenicol or salts of mandelic acid

Terramycin
(Pfizer)
Antibiotic comparable to aureomycin and chloramphenicol

URINARY SYSTEM NEOPLASMS OF

Neoplasms of the urinary sy tem are most frequently encountered in bladder and kidneys (pp 2322 and 2326) With relatively slight dis comfort to the patient the skillful urologist (using direct and indirect methods of visualization) has facilities for making early diagnosi with remarkable exactitude

Employing electrocoagulation for bladder neopla ms and nephrec tomy for those involving the kidney the urologist obtains a high per centage of radical cures with minimum risk provided that the patient is referred when the lesion is subjectively asymptomatic and the most prominent objective finding is persi tent microscopic hematuria (p 2306)

TUMORS OF THE URINARY BLADDER AND KIDNEYS

Practical Management

1 During routine examination note enlargement of kidney (p 2230) microscopic hematuria (p 2306) or persistent pyuria (p 2352)

URINARY ANTISEPTICS

Acriflavin N F
(Abbott National Aniline)

Acridine derivative obtained from coal tar available in official tablets troches and ointments and in powder for preparation of aqueous solutions Only feebly antiseptic in an alkaline urine now obsolete yielding to chloramphenicol aureomycin and sulfonamides

Aureomycin N N R
(Lederle)

Potent antibiotic effective orally against broad bacterial spectrum including gram negative and gram positive cocci and bacilli with chloramphenicol preparation of choice

Chloramphenicol N N R

(Chloromycetin Parke Davis)

Chloromycetin N N R
(Parke Davis)

Preparation of choice with aureomycin, probably preferable against gram negative bacilli

Dihydrostreptomycin N N R
(Merck)

As streptomycin effective but potentially toxic yields preference to aureomycin and chloramphenicol

Gantrisin (NU 445)
(Hoffman La Roche)

A soluble sulfonamide rapidly excreted to produce high urinary concentrations Subject to same criticism as other sulfonamides but to lesser degree Prefer less toxic preparations particularly aureomycin and chloramphenicol

Hexylresorcinol (Caprokol)
(Sharp & Dohme)

Official but feeble urinary antiseptic not comparable to aureomycin and chloramphenicol

Mandelic Acid N F
(Merck Mallinckrodt)

Useful urinary antiseptic in infections due to microbes unable to thrive in an acid urine Especially effective against E coli streptococcus fecalis staphylococcus aureus aerobacter aerogenes aerobacter alkaligenes salmonellae and shigellae For practical use prefer salts of mandelic acid particularly calcium mandelate tablets 0 5 gm (Burroughs Wellcome) For adult dose give 6 tablets four times daily with water intake limited to 1000 cc Maintain urinary acidity at 5 3 or less using chlorphenol red test papers for guidance

Methenamine (Hexamethylamine Urotropin) U S P
(Abbott Merck Merrell Schering)

Feebly effective in acid medium not comparable to aureomycin, chloramphenicol and salts of mandelic acid

Neomycin

As streptomycin

CLINICAL MANIFESTATIONS AND DIAGNOSTIC FEATURES (*Continued*)

Alkaptonuria (*Continued*)

Alkaptonuria is a rare laboratory finding due to the presence of homogentisic acid in urine U ually it exi ts as a harmless anomaly of int rmediate protein m tabolism It is more common in males and is apparently congenital occur ring most often in families that are narrowly inbred

Infrequently alkaptonuria is as ociated with ochronosis (p 3243) Under these circumstances cartilaginous ligamentous and fibrous structures (most apparent in ears corneas and tracheal rings) appear blackened Additionally patients with ochronosis frequently suffer from skeletal di turbances and urolithiasis (p 2311) Each of these complaints is attributable to deposition of abnormal pigmentary material who e presence in blood also causes a false positive Wassermann reaction (p 337)

Pati nts with asymptomatic alkaptonuria require no treatment Those with ochronosis are placed on high carbohydrate feedings (p 671) intramuscular injections of liver extract (p 1048) and oral supplementation with ascorbic acid (p 1049) in an attempt to rid urine of the abnormal intermediate product.

Melanuria

Urine darkens on standing addition of f rric chloride produces gray to black precipitate addition of bromine water gives yellow to black precipitate

Melanuria may accompany any condition in which there is widespread destruc tion of protein Its presence additionally however suggests the pos ibility of a melanotic tumor hence a careful survey is di tinctly indicated since pig mented neoplasms are often of a high degree of malignancy (pp 1563 3221 3225 3275 3297 and 3454)

In rare instanc s melanuria and ochrono is are observed as a result of expo- sure to carbolic acid in a wet dres ing or as an occupational hazard (p 4065) Except for ces ation of exposure to phenol and excision or destruction of melanotic tumors melanuria requires no treatment.

Porphyrinuria

Urine darkens on exposure to light forms red compound with Ehrlich aldehyde test identification requires spectroscopy

Porphyrinuria is a con titutional error in metabolism The porphyrins are ub tituted tetrapyrrilmethenes Coproporphyrin is present normally in urine and stool its excretion is increased in a variety of pathologic conditions including lead poisoning liver insufficiency and anemias Symptomatic or secondary coproporphyrinurias are distingui hed harply from porphyrinurias in which the metabolic anomaly involves the excret on of uroporphyrin whose identi fication is sugg sted by tests mentioned in the chart Uroporphyrinurias may be encountered in congenital photosensitive and adult non photo ensitive varieties

Congenital photosensitive porphyria is an unusual and rare inborn error of metaboli m It is probably present at birth and is inherited as a rece ive Mendelian characteristic The arresting clinical manifestations of congenital porphyria first suggested by the appearance of the urine are es entially cutaneous giving rise to the syndromes known as hydroa aestivale (p 3176) and epidermolysis bullosa (p 3151)

Hydroa aestivale is a rare congenital eruption that is observed during the summer month in childhood In addit on to evidences of urinary excretion of abn rmal porphyrins the young ter reveals vesicular and bullous lesions on exposed surfaces particularly face and arm Lesions tend to recur in sp ing and summer when exposure to ur light is maximum With healing of ve les and blebs progressive and increased ca ring takes place Eventually unle s p otected from exposure to light the child presents cicatricial deformi tie of fingers eyelids bridge of nose and tips of ears Additional evidences of the generalized metabolic di order are revealed in the teeth which take on a red or brownish hue (*erythrodontia*) Later as the child matures enlarge

2 Obtain a catheterized specimen for microscopic examination culture and guinea pig inoculation

3 Inquire as to dysuria (p 2325) or any change in urinary habits

4 In the presence of any positive findings obtain a 24 hour urine specimen *Send to clinical pathologist for cytodiagnosis by Papanicolaou* method

5 Obtain blood for serodiagnosis of malignancy (p 4431) and chest x ray especially for evidences of tuberculosis

6 Refer patient to urologist for cystoscopy (Fig 555 p 2324)

7 Request urologist to obtain biopsy specimen if possible

8 On positive proof of bladder neoplasm discuss electrocoagulation with urologist *before consideration of radical resection* of the viscus

9 On suspicion of supravesical lesion complete survey of urinary tract with catheterization of ureters examination of differential specimens obtained from each kidney and retrograde and intravenous pyelocystography

10 On suspicion of renal neoplasm consider exploratory observation of viscus

11 With definitive proof of neoplasm of kidney refer patient to *urologic surgeon for resection or nephrectomy*

URINE PIGMENTARY CHANGES IN

Passage of dark urine or a specimen which darkens on standing and exposure to air may connote the presence of serious metabolic disturbances ranging from jaundice to anomalies of intermediate protein metabolism

CLINICAL MANIFESTATIONS AND DIAGNOSTIC FEATURES

Pharmacologic

Following ingestion of rhubarb senna or cascara negative tests for bile pigment (p 3686) and other *chromogens* discoloration disappears when drug is discontinued

Concentration

From inadequate fluid intake or excessive fluid loss through excretory channels other than the kidneys (vomiting diarrhea hemorrhage) pigmentary tests negative disappears with adequate hydration

Bile pigment

Yellow discoloration of foam after shaking play of colors when layered with concentrated nitric acid (p 3686)

Alkaptonuria

Urine turns brown to black on standing stains linen after alkalinization foam is luminous in a dark room addition of alkali produces black precipitate and discolors sensitized photographic paper addition of dilute ferric chlorid cause transitory blue discoloration

The management of the e allergic hyper ensitivities requires initial palliation with adrenergens and antihi tamines (p 4212) Later in the free interval between attacks strive to recognize and eliminate the sensitizing modality (p 4175) Attempt desensitization by physio or psycho-therapy and provide prophylaxis with antihistamines or adren ergens (p 4158) With persistent or menacing lesions (angioneurotic edema of tongue uvula or larynx) apply for cortone or ACTH (p 4145)

VACCINIA

[Cowpox]

General Principles of Diagnosis and Therapy

1 The value of artificially produced vaccinia in protection against smallpox has been amply demonstrated since Jenner s first observa tion in 1798 (p 428 Fig 69 pp 430 and 431)

2 Recent attention has been drawn to the disturbing syndrome of post vaccinal encephalomyelitis (p 433) more properly termed an encephalomyelopathy since it is unlikely that pathologic manifesta tions are the result of infection

3 The syndrome of post vaccinal encephalomyelopathy is most likely a manifestation of hyper ensitivity (p 4307) In Belgium Van Bogaert observed sixteen instances with three fatalitie over a span of eighteen years

4 Although the Antitherapeutic Complication (p 4135) is of relatively low incidence its gravity is great More deaths occurred in the 1948 New York City experience for example from postvaccinal encephalomyelopathy than from smallpox itself This statement must not be taken out of text by antivaccinationists since it must be apparent that without prophylactic immunization many citizens of the city and indeed of the country as a whole might have succumbed to the infection

5 The gravity of encephalopathy with its mortality rate of 30 to 40 per cent and its crippling sequels appears sufficient to merit routine use of antihistamine beginning immediately after vaccination and con tinuing for a period of at least three weeks thereafter The manifestations of encephalopathy quite regularly develop between the seventh and fourteenth days after inoculation Prolongation of administration of antihistamine for an additional week would appear completely justified

6 In active treatment of encephalomyelopathy antihistamine may be given parenterally as 1% benadryl using 5 cc (50 mg) intramus cularly or intravenously every three or four hours as needed Simul taneou ly application should be made for cortone (Merck) or ACTH (p 4146) since the high mortality of the complication certainly war rants u e of even limited supplies of these important therapeutic agents

CLINICAL MANIFESTATIONS AND DIAGNOSTIC FEATURES (*Continued*)

Porphyrinuria (*Continued*)

ment of liver and spleen may be noted as well as masculinization in the fem le Pigmentary deposits occur also in bones and during life the e may be detected by strong transillumination

Epidermolysis bullosa resembles hydroa ae tivale in that it is likewise a m ta bolic disturbance of porphyrins In its simplest form, blebs appear at sites of irritation or injury (Fig 891 p 3159) When these blebs rupture and heal there is residual pigmentation but neither scarring nor deformity

A dystrophic variety of epidermoly is bullo a is characteri ed by hemorrhagic blebs over points of pre sure particularly involving hands elbows knees and feet With these there may be muco al lesions particularly in the mouth Healing of hemorrhagic blebs may be associated with severe scarring so that joint function often is impaired

Adult non photosensitive porphyria is ob erved twice as frequently in the male and usually does not become manifest until after the econd or third decades Unlike photosensitive porphyrias who e manife tations are cutaneous the adult non photosensitive form produces its primary effect on the nervous system and abdominal viscera

The clinical manifestations of adult non pho o ensitive porphyria are bizarre The variety of neurologic manifestations is bewildering and may include nervousne s easy fatigue conduct disorders frank psychoses usually of the manic depressive variety delirium coma epileptiform convulsions paralyses of cranial or peripheral nerves with secondary muscle atrophy and contrac tures etc The distribution of lesions is widespread and patchy

To complicate the bizarre neurologic manifestations of adult non photosensi tive porphyria there are often associated vi ceral manifestations which may become apparent through attacks of pain in abdomen or loins with disturbances of bowel function ranging from obstinate constipation to intractable diarrhea The *diagnosis* of the adult non photo ensitive varieties of porphyrias becomes obvious only when urine examinations reveal the pathognomonic features of uroporphyrinuria Adult non photosen itive varieties of porphyrinuria have a favo able prognosis which unfortunately is not shared by photosensitive syndromes The latt r have a high mortality rate approximating 80 per cent within five years of onset of symptoms Although authorities have little con fidence in therapeutic measures the grave prognosis of youthful photo ensi tive varieties of porphyrinuria requires that the practitioner make every effort to protect his patient

By means of clothing or solar protective lotions and ointments (p 3140) expo sure to light is strictly avoided On the ba is that the disturbance may be an allergic hypersens tivity reaction to solar energy prescribe antihistamines (p 4212) Additionally becau e of the ominous prognosis of youthful forms apply for cortisone or ACTH on a probatory and experimental basis Sympto matic reduction of porphyrinuria has been reputed to follow intravenous injections of calcium (p 603) intramuscular injections of liver extract (p 1048) ingestion of a high carbohydrate diet (p 672) and supplementary additions of niacin (p 625) and ascorbic acid (p 1049)

URTICARIA AND ANGIONEUROTIC EDEMA

Urticarias and attacks of the more alarming angioneurotic edema occur with great frequency in private practice (Fig 984 p 3347) In many instances these dermatoses are representations of psychogenic allergy Again they may result from exposure to heterologous serum digestants drugs and physical agents

Peru to avoid infection by descending below an altitude of 2 000 feet or ascending above 9 000 feet to spend the night. If it is necessary to spend the night in an infected area reasonable security against infection can be obtained by screening (Pinkerton in Cecil s Textbook of Medicine 7th Ed p 100)

2 Individual prophylaxis also may be accomplished by use of insecticides particularly DDT aerosol bombs (p 4373)

Immediate Care

1 Excellent results are reported from administration of streptomycin to patients in the evolutionary phase of acute progressive anemia (Carrion s disease) and in the phase of the verruca eruption There was immediate improvement of severe anemia and clinical cure by the end of treatment Bartonella disappeared from peripheral blood within the first three to five days of treatment and there was rapid regression of verrucal lesions Penicillin also appears to produce good results in halting the course of bartonella anemia Although no clinical reports are currently available it would appear wise to supplement streptomycin therapy with daily deposits of 300 000 to 600 000 units of procaine penicillin G in aqueous suspension or oil

2 The bactericidal action exhibited by streptomycin is not found in arsenicals sulfonamides or para aminobenzoic acid

3 Presumably if streptomycin is effective probatory therapy with aureomycin or chloramphenicol merits trial because of lesser toxicity and greater ease of administration of these more recently developed antibiotics

4 In addition to antibiotic therapy patients with acute progressive anemia are entitled to oral administration of iron (p 1048) intramuscular injections of liver extract (p 1048) and whole blood transfusions (p 3778) where indicated

VIRUS DISEASES

Virus diseases which do not occur often or are as yet encountered only in animals are tabulated below

Virus or Disease	Occurrence	Symptoms	Treatment
Bunyamwera virus	Healthy inhabitants of Uganda	Not yet observed as clinical disease	Aureomycin/ chloramphenicol will merit trial
Bwamba fever	Uganda	Fever headache generalized pain, conjunctivitis generalized dermatosis	Symptomatic
[illegible]lifornia [illegible]n Reeves)	In Aedes dorsalis and Culex tarsalis	Clinical disease not described	

VENEZUELAN EQUINE ENCEPHALITIS

General Principles of Diagnosis and Therapy

1 Venezuelan equine encephalitis is primarily a viremia of horses and mules However, it may be transmitted to humans by a mosquito vector producing a mild clinical syndrome

2 In the prodromal phase human patients complain of manifestations resembling influenza with mild headache and fever Later they develop intestinal disturbances tremors myalgias diplopia and lethargy

3 After three to five days symptoms and signs abate and the patient makes a prompt and complete recovery

4 Neutralizing antibody is found in the blood of recovered patients as well as in many who give no history of having had the disease

5 A formalin inactivated vaccine has been prepared from infected chick embryos This has been used in Venezuela for prevention of the disease in horses and might possibly prove useful if a human epidemic broke out

VERNAL CONJUNCTIVITIS

Principles of Diagnosis and Therapy

1 Regard vernal conjunctivitis as an acute histamine type hypersensitivity (Fig 331 p 1650)

2 Avoid antibiotics particularly hyperallergens such as sulfonamides locally or systemically

3 Prescribe antihistamines orally (pyribenzamine or benadryl 200 mg daily) and antistine 0 5% ophthalmic solution locally

VERRUGA PERUANA

(Oroya Fever Carrion s Disease Bartonellosis)

General Principles of Diagnosis and Therapy

1 Verruga peruana is a specific disease caused by a minute rickettsial like micro organism *Bartonella bacilliformis* (Fig 60 p 385)

2 *The vector is probably the sandfly*

3 In laboratory experiments streptomycin has a potent bactericidal action on the invading microbe

Practical Management

Prophylaxis

1 Since the sandfly does not emerge from the rocky caves in which it lives until after dark it is possible for visitors in the infected areas in

VIRUS HEPATITIS

[Catarrhal Jaundice Infectious Hepatitis Epidemic Hepatitis]

General Principles of Diagnosis and Therapy

1 The term virus hepatitis is preferred to that of catarrhal jaundice previously employed (p 1979) It clearly indicates the etiologic agent and hence is more meaningful than the descriptive terms catarrhal and jaundice

2 Of the varieties of infectious jaundice virus hepatitis is most commonly encountered by the practitioner Spirochetal hepatitis (Weil s disease) is exceedingly rare in civilized communities (p 4527) and homologous serum jaundice (clearly differentiated by the history of antecedent transfusion pla ma infusion or inoculation with yellow fever vaccine) soon may be eliminated by irradiation of biologicals intended for parenteral use (p 4358)

3 Experiments on human volunteers indicate that the incubation period of virus hepatitis averages twenty five days the pre icteric phase five days the icteric pha e an average of four weeks with persistence for ten weeks and even several months in extreme instances

4 More frequently than was previou ly suspected virus hepatitis terminates in hypertrophic cirrhosis In a few instances carcinomatous change also has been noted

5 A virulent variety of virus hepatitis has been reported from Den mark It occurs primarily in women after the menopause and has a fatality rate approximating 50 per cent with terminal ana arca and ascites

6 To the best of current knowledge the virus producing epidemic hepatitis is not susceptible to any known antibiotic Protective antibody however is present in gamma globulin

Practical Management

Prophylaxis

1 The high rate of infectivity of virus hepatitis and the prolonged period of incubation indicate the wisdom of protecting all contacts by injection of gamma globulin using 0 06 to 0 12 cc per pound of body weight (approximately 10 cc intramuscularly for the average adult weighing 150 pounds) Gamma globulin insures protection if given before the sixth day preceding onset of the pre icteric phase Immunity persist for six to eight weeks

2 Since the disease is quite likely stool borne attention to personal hygiene of patient and contacts is e sential to interruption of the infectious cycle All should be cautioned to wash hands thoroughly after stool and before food handling

Immediate Care

1 If the patient is seen in the pre icteric phase of the disease and gamma globulin is readily available try to modify the course by intra

Virus or Disease	Occurrence	Symptoms	Treatment
Coxsackie (Dalldorf) virus disease	New England	Fever headache nausea stiffness of neck pain drowsiness sore throat positive Brudzinski or Kernig sign	Try aureomycin and chloramphenicol
Fort Bragg fever *(pretibial fever)*	Texas	Pain fever unusual eruption of 2 to 5 cm blotches usually on pretibial areas relative leukopenia	Symptomatic
Infectious anemia *of horses*	Specific viremia of horses occasionally transmitted to man	Fever anemia pain diarrhea	Aureomycin/chloramphenicol ment trial
Ovine pustular dermatitis	Specific disease of sheep occasionally transferred to man	Vesiculopustular eruption headache lymphadenitis	Symptomatic
Ovine encephalomyelitis (louping ill)	Disease of sheep occasionally transmitted to man	Fever encephalomyelitic manifestations	Prophylaxis by tick control Aureomycin/chloramphenicol ment trial
Rift valley fever *(enzootic hepatitis)*	Acute viremia of sheep occasionally transferred to man	Fever pain in extremities and joint leukopenia	Symptomatic
Swineherd's disease	In young adult farm hands	Gastro enteritis meningeal irritation maculopapular eruption	Aureomycin/chloramphenicol ment trial

VIRUS DYSENTERY

[Epidemic Nausea Vomiting and Diarrhea Epidemic Dysentery]

General Principles of Diagnosis and Therapy

1 Epidemics of gastro enteritis have been reported from several localities in which the usual causative organisms (Salmonellae and Shigellae) have not been demonstrable

2 In places various investigators have isolated one or more filtrable infectious agents Epidemic gastro enteritis a specific infectious disease was found to be the most common diarrhea in New York State in 1946 and 1947

3 At present there are no specific laboratory aids to diagnosis The disease is self limited and requires only symptomatic therapy

3 Virus pneumonitis runs a completely atypical cour e although eventual recovery is the rule

4 The specific pneumonitis virus is insensitive to penicillin sul fonamide and streptomycin It reveals striking sensitivity both to aureo mycin and chloramphenicol

Practical Management

Immediate Care

1 Prescribe a priming dose of aureomycin or chloramphenicol approximating 25 mg per kilogram of body weight for the former (3 5 gm for average adult weighing 150 pounds) and 50 mg per kilo gram for latter (7 gm) To les en gastric irritation suggest that patient swallow 2 products every few minutes well diluted with milk tea ice cream fruit juice soup or cream cheese

2 Institute non specific therapy for management of infected patient (p 67)

3 Warn contacts of high infectivity of disease Have nurses and other attendants ma k while in immediate vicinity of patient

4 Avoid symptomatic drug treatment if possible analgesic anti pyretics may increa e gastric irritability and opiates depre s cough reflex favoring retention of secretion in bronchial passages If pressed pre cribe simplest expectorant (liquor ammonium anisatis 2 cc well diluted every two to three hour)

Continuing Care (Favorable Course)

1 Order daily maintenance doses of aureomycin or chloramphenicol Of former 1 to 2 gm in 4 divided portions suffices for majority of infections Of chloramphenicol use larger doses approximating 2 to 3 gm

2 Continue maintenance doses for several afebrile days to avoid relapse

Continuing Care (Unfavorable Course)

1 Double daily maintenance doses of antibiotics

2 If either antibiotic produces gastric irritation substitute other

3 If stomach is intolerant of both antibiotics consider intravenous injection of 100 mg of aureomycin using preparation labeled for intravenous use in diluent supplied by manufacturer

4 Supplement aureomycin/chloramphenicol with penicillin Deposit priming intramuscular dose of 600 000 units of crystalline procaine penicillin G in aqueous suspension Repeat after eight twelve or twenty four hour intervals as indicated

Continuing Care (Progressively Unfavorable Course)

1 If patient is restle s cyanotic dyspneic or racked by cough inaugurate oxygen therapy by mask or tent (p 3827)

2 Maintain nutrition with concentrated high-calory diet chosen according to patient s taste (p 671)

muscular injection of at least double the prophylactic dose i e 20 cc deposited intramuscularly

2 In view of the possible length of incapacitation the long period of convalescence and the frequent incidence of late cirrhosis institute probatory anti infective therapy with aureomycin or chloramphenicol since these of all antibiotic agents have virucidal potential In view of the insensitivity of the virus give large doses approximating 4 to 6 gm daily

3 Contrary to previous advice use a high calory diet with the normal quota of fat

4 To prevent hepatic cell destruction start immediately to administer lipotropic principle Give syrup of choline dihydrogen citrate in doses of 8 to 12 cc daily or 2 to 4 capsules each containing 250 mg of choline

5 *To prevent hemorrhagic disturbances* administer vitamin K Give intramuscular injections of menadione 2 5 mg once or twice daily

Continuing Care (Favorable Course)

1 Continue routine for a period of no less than two and preferably three weeks Early resumption of activity and premature termination of bed rest increase the *severity of symptoms* favor recurrence and delay recovery

Continuing Care (Unfavorable Course)

1 With persistent vomiting and resultant dehydration and hypoproteinemia establish an intravenous drip Give daily 1000 cc of 5% dextrose in saline one or two units of plasma or of a protein hydrolysate 100 mg of thiamine hydrochloride 100 mg of ascorbic acid and 2 5 mg of menadione (p 4235)

2 Follow progress of disease by daily determinations of urinary *urobilin and urobilinogen*

VIRUS PNEUMONITIS

(Atypical Pneumonia)

Principles of Diagnosis and Therapy

1 Virus pneumonitis is a specific abacterial respiratory infection serologically characterized by production of cold hemagglutinins and streptococcus MG agglutinins These laboratory criteria provide the basis of a definitive subclassification of virus pneumonitis and distinguish it from other forms of acute pneumonitis (p 2185 and Fig 497 p 2187)

2 *In* private practice virus pneumonitis is the most frequently encountered infection of the pulmonary alveoli (p 2188) Army statistics confirm the previously expressed opinion that in proportion to lobar pneumonia virus pneumonitis is encountered *30 to 1*

presently incompletely established but it probably involves jungle monkeys

2 The incubation period in human volunteers is three to six days following bite of infected vector

3 Severity of the disease varies from asymptomatic infections which are nevertheless immunizing to the classical clinical syndrome (p 478) carrying a mortality rate as high as 60 per cent

4 Laboratory diagnosis is established by isolation of virus requiring very special technics and development of virus neutralizing bodies in increasing titer

5 An attenuated chick embryo growth of virus has been harvested by the United States Public Health Service for prophylactic vaccination Omission of human serum has eliminated contaminating icterogenic organism of homologous serum jaundice (p 4358) which raised such havoc with the armed forces in World War II

Practical Management

Prophylaxis

1 Production of artificial active immunity by injection of 0 5 cc of vaccine only one inoculation is necessary

2 Following injection approximately 5 per cent of patients develop malaise headache and fever on the seventh day Immunity as determined by specific neutralizing bodies is manifested on the seventh to ninth days The duration of immunity is probably at least four years

3 Individual prophylaxis also can be accomplished by avoidance of mosquito bites through liberal use of insecticides (p 4373)

Immediate Care

1 Notify health authorities

2 Remove patient to a special hospital equipped for care of yellow fever if possible

3 Immunize all contacts

4 Suggest probatory anti infective treatment with aureomycin or chloramphenicol which are demonstrably virucidal fortified with penicillin for possible synergistic activity

5 Inaugurate symptomatic therapy (pp 68–73) Suggest measures to prevent dehydration and hypoproteinemia Set up intravenous drip of 5% dextrose in sterile distilled water Add protein hydrolysates (p 4235) and plasma or whole blood if indicated

6 Prevent avitaminosis and bleeding tendency by addition to drip of soluble vitamins particularly K

7 Attempt to obtain human homologous convalescent serum for addition to intravenous drip or for intramuscular injection (p 4260)

3 Collect sputum Examine direct spreads for fungi (Fig 75 p 486 Fig 76 p 487) Use gram stain for predominant bacteria (p 52) and carbol fuchsin stain for tubercle bacilli (p 52) Send specimen to clinical pathologist for repetition of tests cultures and animal inoculation Pneumonitis due to tubercle bacilli and fungi may closely simulate syndromes of acute or protracted virus pneumonitis

4 If course of disease continues unabated and other microbic in aders are not demonstrable persist with combination of aureomycin/chloramphenicol and penicillin doubling and redoubling doses until recovery has been effected

VISCERAL ANGIITIS

Principles of Diagnosis and Therapy

1 Regard visceral angiitis as a chronic tuberculin type hypersensitivity (p 4169) with predominant peripheral vascular lesions

2 Treat as atypical verrucous endocarditis (p 4311)

THE XIPHOSTERNAL CRUNCH

A crunching sound heard best over the lower sternum and the ensiform cartilage is noted in approximately one healthy man in five The xiphosternal crunch usually occurs during systole though it may accompany either heart sound Its intensity is slight in approximately half the patients examined moderate in a little more than one third and quite marked in slightly more than one fifth The crunch is confined to sternal and ensiform regions in slightly less than one fifth of all observations it is transmitted to the left in slightly more than four fifths being heard as far as the apex in an occasional instance

The xiphosternal crunch bears no relationship to cardiac disease general development or pulse rate It has no pathologic significance Its importance lies in its recognition as a mere acoustic phenomenon which must not be mistaken for an organic cardiac murmur (p 973) or a pericardial friction rub (p 3549)

YELLOW FEVER

[Virus Amaril Fievre Jaune Gelbes Fieber Jungle Yellow Fever]

Principles of Diagnosis and Treatment

1 Yellow fever is a viremia In urban yellow fever the vector is a mosquito Aedes aegypti in jungle yellow fever the virus cycle is

INDEXES

An Integrated Practice of Medicine

INDEX OF DIFFERENTIAL DIAGNOSIS BY MAIN PRESENTING SIGNS AND SYMPTOMS

NOTE The page number given after each symptom leads to the tabl containing diseases or conditi ns from which the sym ptom in question can be differentiated
A bold face page number indicates that an entire table is concerned with the symptom a pag other than boldface indicates discussion within the tables

GENERAL INDEX, VOLUMES I TO IV

NOTE Bold face page numbers indicate main discussions

INDEX OF ILLUSTRATIONS

NOTE Bold face page numbers indicate colored illustration.

INDEX OF ILLUSTRATIONS

NOTE Bold face page numbers indicate colored illustration

INDEX TO THE PROGRESS VOLUME

INDEX TO THE PROGRESS VOLUME